Synthetic Applications of Hydrazones

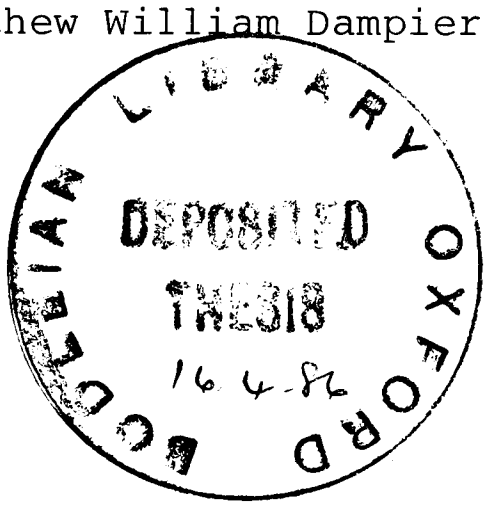
A thesis submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

by

Matthew William Dampier Perry



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Synthetic Applications Of Hydrazones

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ABSTRACT

This thesis describes investigations of reactions of hydrazones and their N-anions via the imino carbon atom; these reactions show umpolung reactivity. The conversion of the derived azo products into synthetically useful compounds (e.g. 4-ketoesters, 4-ketoacids, 4-ketonitriles, alkanes, amines) is also described.

Reactions of t-butylhydrazone anions with enoic esters are described. 4-t-Butylazoesters were formed on reaction with methyl crotonate. The 4-t-butylazoesters derived from aldehyde t-butylhydrazones were converted by tautomerisation of the azo function and hydrolysis of the resultant t-butylhydrazone to 4-ketoesters or 4-ketoacids in 47-60% yield. Other Michael type electrophiles investigated gave negligible yields of C-adducts.

t-Butylhydrazones of aliphatic aldehydes were found to give ene adducts with methyl acrylate or acrylonitrile on reflux in xylene for 24h. The resultant azo compounds were converted into 4-ketoesters (75-90%) or 4-Ketonitriles (18-75%) by tautomerisation and hydrolysis. Other potential enophiles investigated did not give C-adducts.

A synthesis of a t-butylazoalkene from an aldehyde t-butylhydrazone and benzaldehyde by addition and dehydrative elimination is described. The reduction of t-butylazoalkenes with zinc-acetic acid is described.

The C-alkylation of tritylhydrazone anions with alkyl halides gave tritylazoalkanes. Tritylazoalkanes decomposed by homolytic fragmentation with dinitrogen evolution above -20°C. Trapping with ethanethiol of the resultant radicals gave alkanes in 27-69% yield.

The last section describes investigations of the anions of various secondary alkyl hydrazones for C-reaction, and attempted reduction of the resultant azoalkanes to amines Isopropyl- and cyclohexylhydrazones gave low yields of C-adducts. 2,4-Dimethylpent-3-yl- (DMP) and 3,3-dimethylbut-2-ylhydrazones (TBM) gave good yields of C-adducts. Direct reduction of the azoalkanes to amines was not achieved. Azoalkanes derived by alkylation of ketone DMP or TBM hydrazones were tautomerised and hydrolysed to hydrazines in low yield. Reduction of a so-formed hydrazine gave an amine, but in low overall yield (14%).

Great are the works of the LORD,

Studied by all who have pleasure in them.

Psalm 111[2]

Acknowlegements

This thesis would not have been possible without the help of many people. I would like to thank the following in particular:

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Abbreviations

DME	dimethoxyethane
DMSO	dimethylsulphoxide
ether	diethylether
HMPT	hexamethylphosphorous triamide
petroleum	light petroleum, fraction 30-40^{o}
TFA	trifluoroacetic acid
THF	tetrahydrofuran
n. m. r.	nuclear magnetic resonance
n. O. e.	nuclear Overhauser effect
min.	minutes
h.	hours
^{o}	degrees Celsius

Contents

CHAPTER 1

Introduction

This thesis is concerned with the development of synthetic methods based upon hydrazones. Specifically it describes the use of hindered hydrazones and their anions to give products derived from reaction at the imino carbon atom and their conversion to compounds formally derived by umpolung.

Umpolung

The principle of umpolung,[1,2] that is polarity inversion, is a central one in the development of synthetic methodology. The importance of umpolung arises because the most common (and most important) heteroatoms (oxygen, nitrogen) confer the same pattern of polarity upon organic molecules. This pattern of polarity is produced by:

(1) The electronegativity of these heteroatoms which stabilises a negative charge on the heteroatom, and polarises uncharged species, activating them to attack.

(2) The availability of lone pairs of electrons on the heteroatoms which can stabilise a positive charge on the carbon atom to which the heteroatom is bonded, or can act as electron pair donors toward Lewis acids.

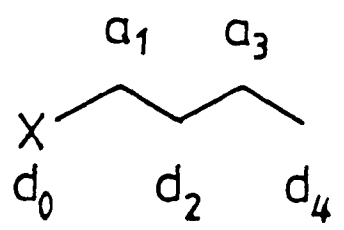
(3) The transmission of effects (1) and (2) through polyene chains.

The combination of these effects confers an alternating

pattern of electron pair acceptor and donor sites on common oxygen and nitrogen functionalised molecules:

The result of this pattern of reactivity is that certain relationships of functional groups are easy to construct by polar reactions (1,1; 1,3; 1,5; 1,2n+1) whereas others (1,2; 1,4; 1,6; 1,2n) can not be formed without some form of umpolung.

generally:



a acceptor sites

d donor sites

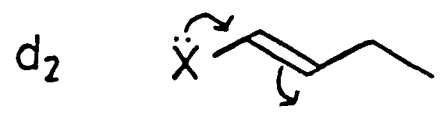
examples:

X=O⁻ alkoxide

$=NR_2$ amine

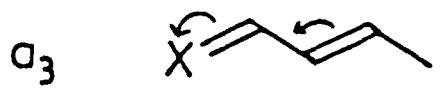
X=O carbonyl

$=N^+R_2$ im inium ion



X=O⁻ enolate

$=NR_2$ enamine



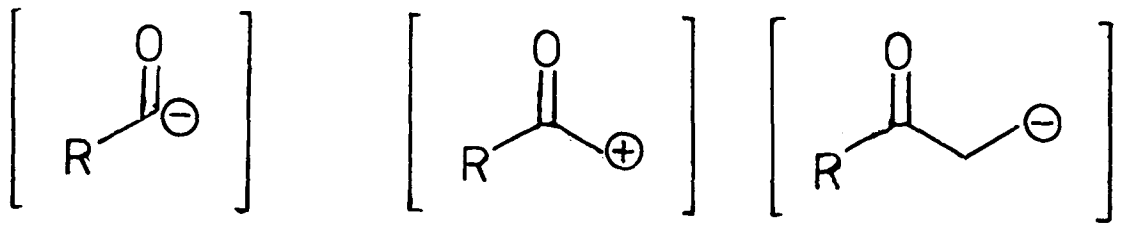
X=O enone

The limitations of simple polar reactions have resulted in considerable importance being placed on methods to obtain 1,2n functionalised molecules. Methods that have been used include free radicals,[3-7] oxidations (epoxidation generates 1,2- functionalised systems, ozonolysis of cyclic olefins with even numbered ring sizes generates 1,2n dicarbonyl compounds), the use of naturally occuring 1,2n functionalised molecules[8] (this is analogous to the use of naturally occuring chiral molecules for synthesis,[9] and it takes advantage of biochemical techniques for

umpolung[10,11]) and umpolung methodology.

The fourth category, that of synthetic umpolung methodology, has been a major area of research since Corey and Seebach[12] introduced dithianes as acyl anion equivalents. The description of retrosynthetic analysis[13] as a powerful method for designing syntheses and the recognition therein of synthons (synthetic equivalents) has been a spur to the development of reagents that can act as unusual (including umpolung) synthons.

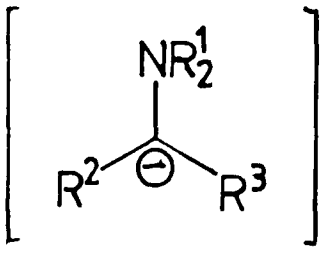
The carbonyl group is arguably the most important functional group of synthetic chemistry. In consequence of this many different approaches to the umpolung of carbonyl systems have been developed; common umpolung synthetic equivalencies include acyl anion equivalents (I),[14,15] enolonium ion equivalents (II),[16] and homoenolate equivalents, (III).[17,18]



(I) (II) (III)

The amino function arguably follows the carbonyl group in order of synthetic importance, and therefore umpolung methodology has been developed for amines; common umpolung equivalences for amines include: α-amino anions (IV)[19-21,7] and β-amino cations (V).[22]

Umpolung techniques have also been developed for other functionality.[23-26]



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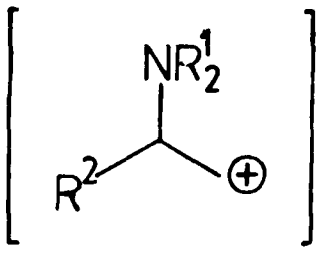


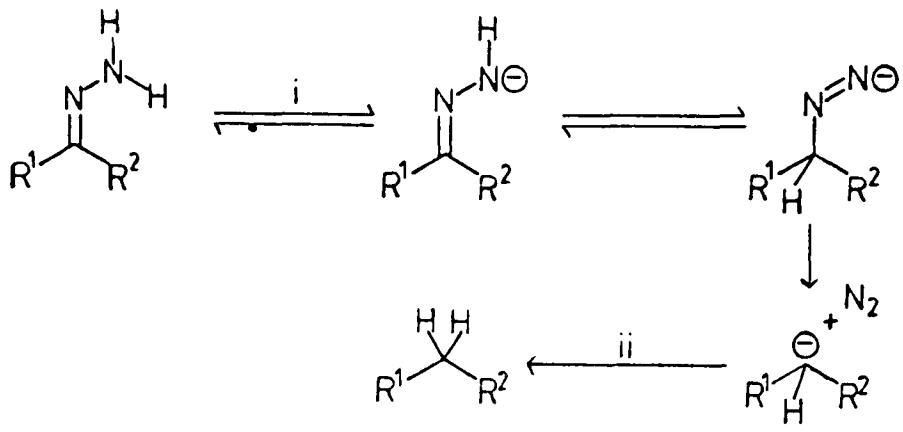
(V)

Of the many methods for reactivity umpolung that have been published few have progressed into being standard synthetic procedures. Many of the methods currently available require the use of strong bases, or other forcing conditions. Other problems associated with present methodology include the difficulties of scaling up the procedures, problems arising from demasking the operator functionality, and the use of expensive or toxic reagents. The scope for improvement is thus considerable.

The Chemistry of Hydrazone Anions

The first synthetically useful procedure involving hydrazone anions was the Wolff-Kishner reduction.[27] This reaction of unsubstituted hydrazones or semicarbazones with bases (usually ethoxide at 180-200°, but sometimes potassium hydroxide in DMSO at room temperature) is believed to proceed *via* hydrazone anions.[28] (scheme 1)

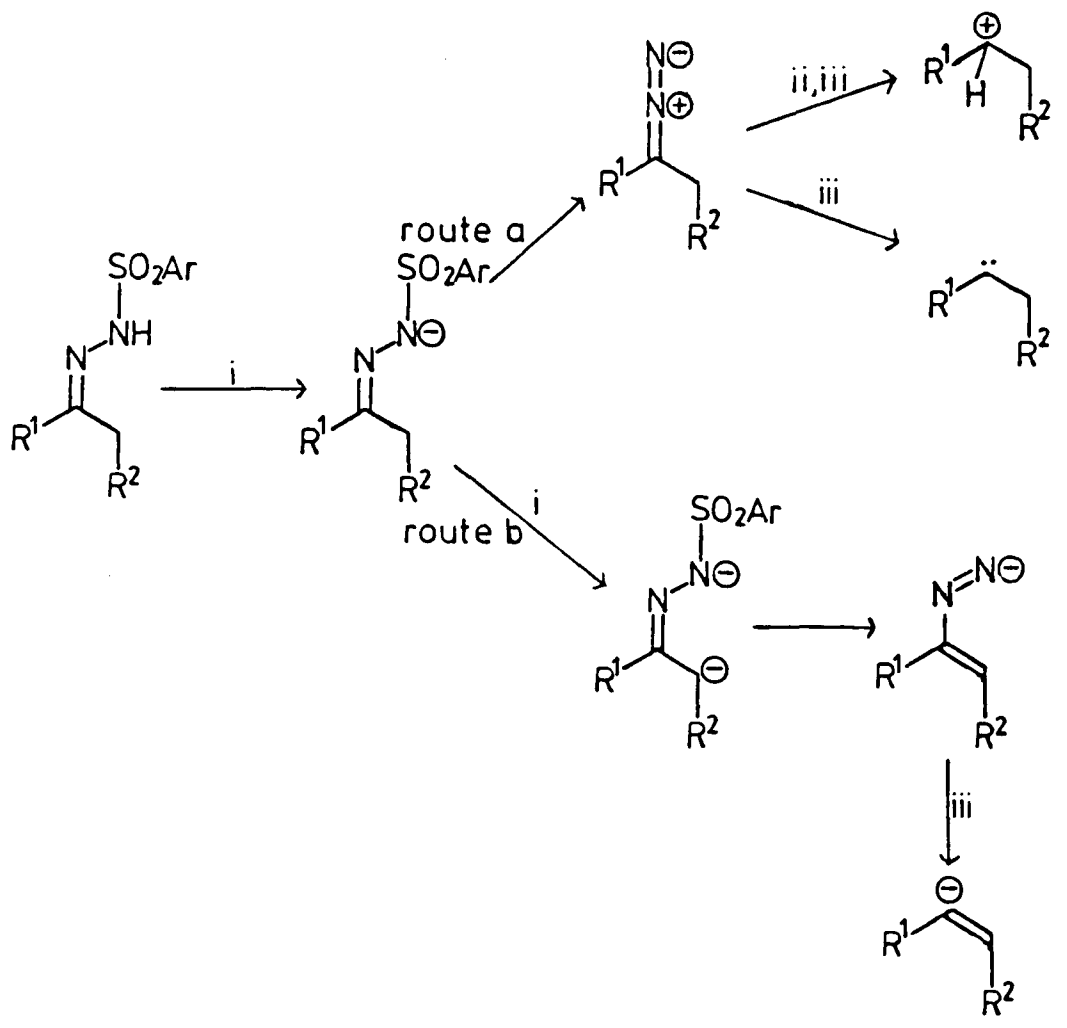
The dianions of unsubstituted hydrazones[29] have been monoalkylated on nitrogen by adding 1 equivalent of alkylating agent. Excess alkylating agent gave rise to *N*,*N*-dialkyl hydrazones. No products from *C*-alkylation were observed.



i B^- ii BH

Scheme 1

The anions of arylsulphonylhydrazones have been extensively studied notably in the Bamford-Stevens[30] and Shapiro[31,32] reactions. (scheme 2)



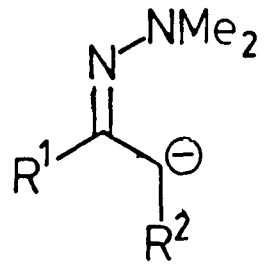
route a Bamford-Stevens route b Shapiro

i B^- ii H^+ iii $-N_2(g)$

Scheme 2

The hydrazone anions present in the Bamford-Stevens and the Shapiro reactions have never been observed to react at the imino carbon atom. Reaction at this carbon atom is, however, observed after nitrogen loss.

The α-carbon of hydrazones is activated analogously to the α-position of carbonyl compounds, although the activation is considerably less and stronger bases are required to deprotonate hydrazones than carbonyl compounds. Corey and Enders[33] have used the anions of dimethylhydrazones (VI) as enolate equivalents. Enders[34] has extended this to chiral N,N-dialkylhydrazones (VII) which gave excellent enantioselectivities on alkylation if very low temperatures (e.g. -100°)[34] were used.



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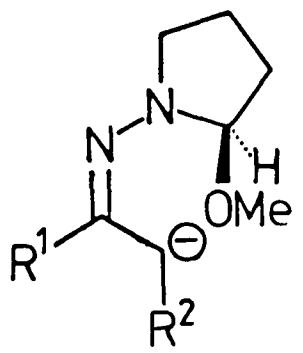

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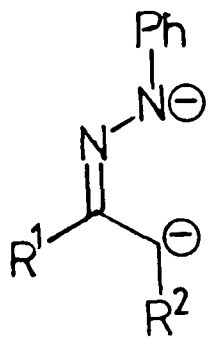
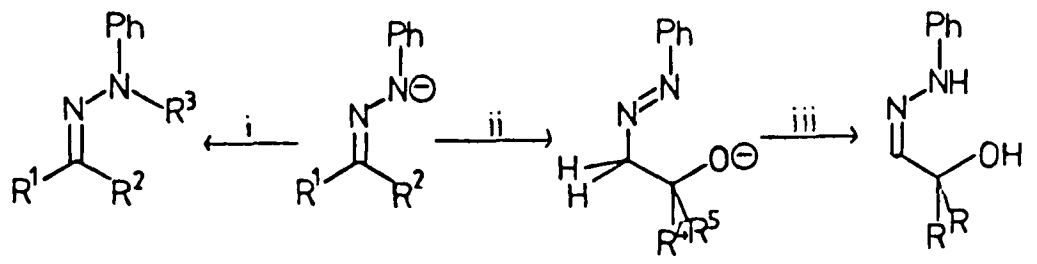


(VIII)

The dianions of phenylhydrazones (VIII) have also been shown to react with alkylating agents at the α-carbon atom.[35]

Monoanions of phenylhydrazones have been shown to react on nitrogen with alkylating agents under both homogeneous[36] and phase-transfer[37] conditions. In contrast, the anion derived from benzeneazomethane (equivalent to that derived

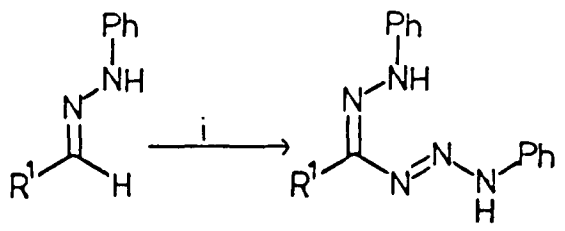
from formaldehyde phenylhydrazone) reacted with aldehydes and ketones to give 40-77% yields of the phenylhydrazones of α-hydroxyaldehydes.[38] (scheme 3) The anions of higher aldehyde phenylhydrazones do not give C-adducts with aldehydes and ketones.[39]



i R^3X ii $R^1 = R^2 = H$, R^4COR^5 iii H^+

Scheme 3

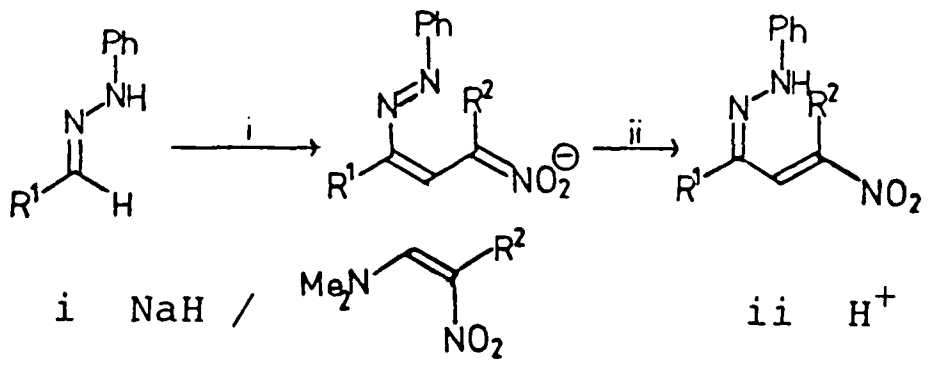
Aldehyde phenylhydrazones have been shown to react with phenyl azide under base catalysed conditions to give N-aminoformazans.[40] (scheme 4) This could involve initial reaction on N followed by rearrangement.



i PhN_3 / EtOH / EtONa

Scheme 4

The anions of aldehyde phenylhydrazones give C-adducts with β-dimethylaminonitroolefins.[41] (scheme 5)



i NaH /

Scheme 5

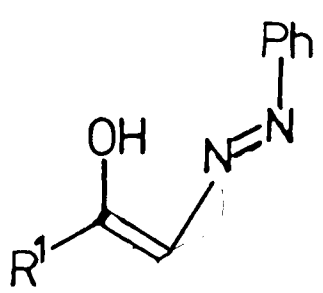
The anions of t-butylhydrazones have been shown to give N-silyl compounds on reaction with dialkylsilyl-difluorides.[42]

The anions of hydrazones have received considerable investigation. The work of Enders has developed the α-anions of N,N-dialkylhydrazones into extremely valuable enolate equivalents.[43] The Shapiro reaction is a powerful method for the synthesis of olefins, and has found application in natural product synthesis.[44] The reaction of hydrazone anions on carbon has been demonstrated for a few isolated examples, but prior to our investigations it had not been developed into a general method.

Reactions of Hydrazones at the Imino Carbon Atom

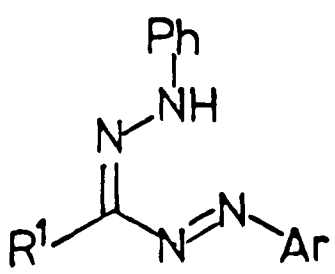
The few reactions of phenylazoanions on carbon are the only previous examples of C-reactivity of hydrazone anions. There are however several reactions of unionised hydrazones where reaction with electrophiles occurs on carbon.

Hydrazones activated by an α-keto group have been shown to react with formaldehyde on carbon,[45] presumably via an azoenol. (IX)



(IX)

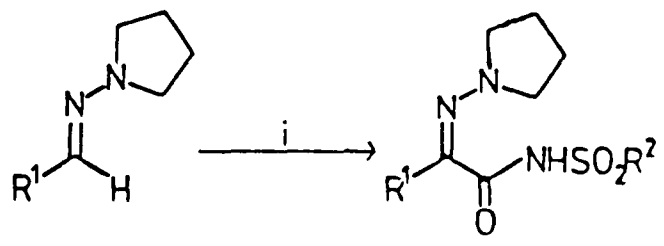
Diazonium salts have been shown to couple with aldehyde phenylhydrazones on carbon to give formazans (X),[46] nitrosating agents give analogous nitrosazones (XI).[47] These reactions may proceed *via* initial reaction at nitrogen, followed by rearrangement.[48]



(X)

(XI)

N-Aminopyrrolidine hydrazones have been described as aza-enamines. They have been shown to react on carbon with strongly electrophilic species.[49] (Vilsmeier reagents, sulphonyl isocyanates) (scheme 6) Similar results have described for a variety of aromatic aldehyde dialkylhydrazones with chlorosulphonyl isocyanate.[50]

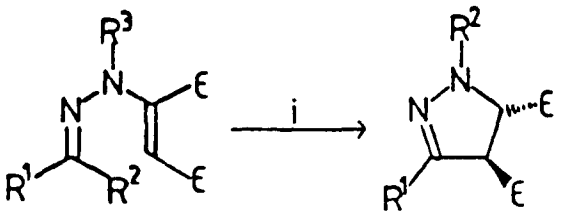


i $R^2SO_2N=C=O$

Scheme 6

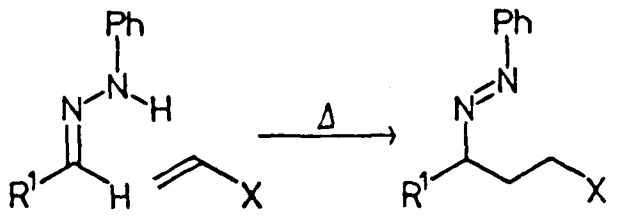
Reaction of hydrazones at carbon has also been demonstrated during some electrocyclic processes. *N*-Vinylhydrazones have given heterocycles on heating.[51,52] (scheme 7) More interestingly aldehyde phenylhydrazones

have been shown to react with enophiles to give C-adducts.[53,54] (scheme 8)



i Δ, R^2=H E=CO_2R^4

Scheme 7



X=CO_2Me, Ph, CN

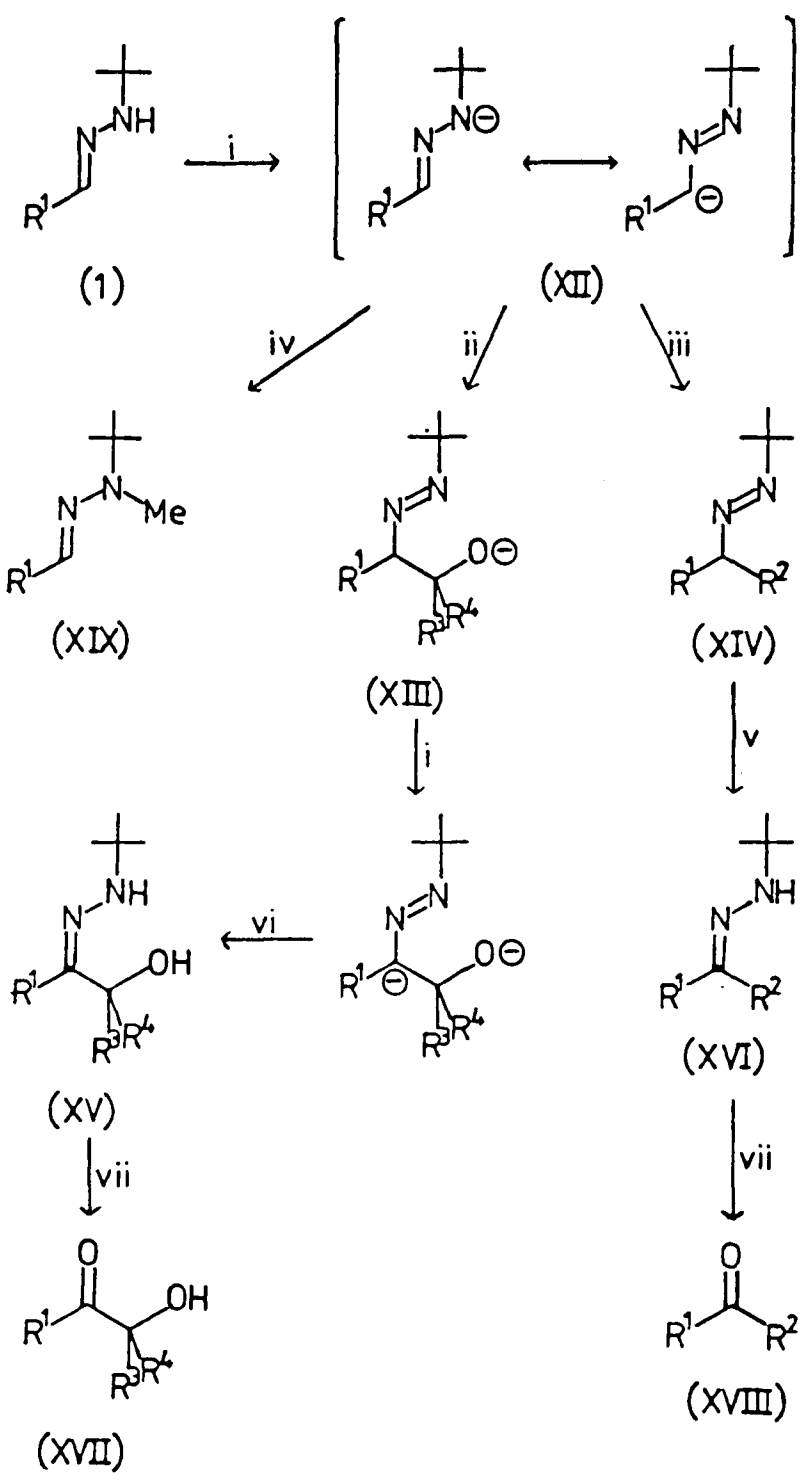
Scheme 8

The limited ability of hydrazones to react at carbon has been known for many years, as has the potential of the products to be diverted into either amines or ketones.[53] Despite this neither of these possibilities has been exploited synthetically before.

Hindered Hydrazone Chemistry

The general principle of umpolung using hindered hydrazones has been established.[55,56] Aldehyde t-butylhydrazones (1) have been shown to give anions (XII) that act as acyl anion equivalents, giving α-hydroxyketones (XVII) or ketones (XVIII) with aldehydes and ketones or alkyl halides respectively. The initial adducts (XIII,XIV) were tautomerised to the hydrazone form (XV,XVI) under either basic or acidic conditions. The hydrazones (XV,XVI) were then hydrolysed with aqueous oxalic acid to the α-

hydroxyketones (XVII) or ketones (XVIII). (scheme 9) Water was found to protonate the hydrazone anions on nitrogen. Methyl iodide gave N-methyl hydrazones(XIX) by N-alkylation, thus the steric effect of the t-butyl group requires a moderately sized electrophile to produce C-alkylation.

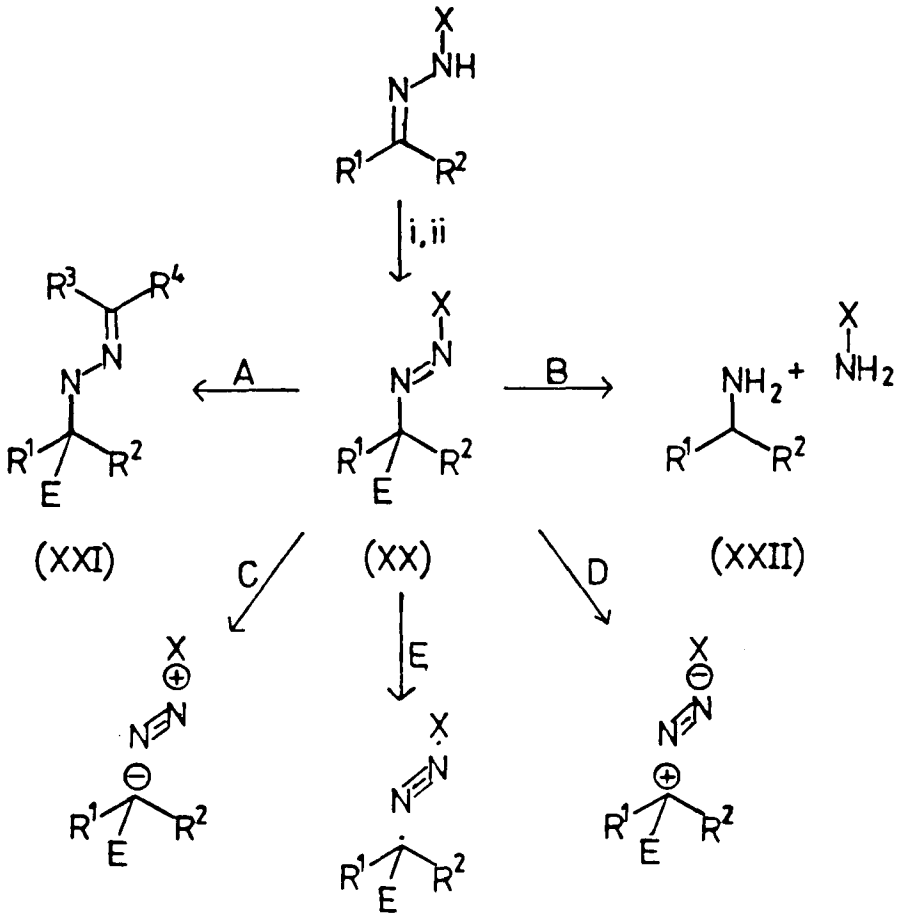


i n-BuLi ii R^3COR^4 iii R^2X iv MeI

v TFA vi H_2O vii $(COOH)_2$ / H_2O / Et_2O

Scheme 9

A consideration of the azo products (XX) produced by reaction of hindered hydrazone anions with electrophiles suggested that these intermediates could be diverted to products other than ketones. (scheme 10) This would enable hydrazones to act as a variety of umpolung equivalents.



i B^- ii E^+

Scheme 10

The synthesis of ketones involved tautomerisation of the azo compound to a hydrazone. (XV,XVI) Tautomerisation of the azo compound (XX) in the opposite sense (path A) would lead to a hydrazone (XXI) which could then be hydrolysed to give a hydrazine. Such a process would represent a formal α-hydrazino anion.

Reductive cleavage (path B) would provide a convenient

synthesis of primary amines (XXII) by a formal α-amino anion equivalent. It would allow aldehydes and ketones to be used as the starting point for amine synthesis, in a transformation that would represent an overall alkylation and reductive amination.

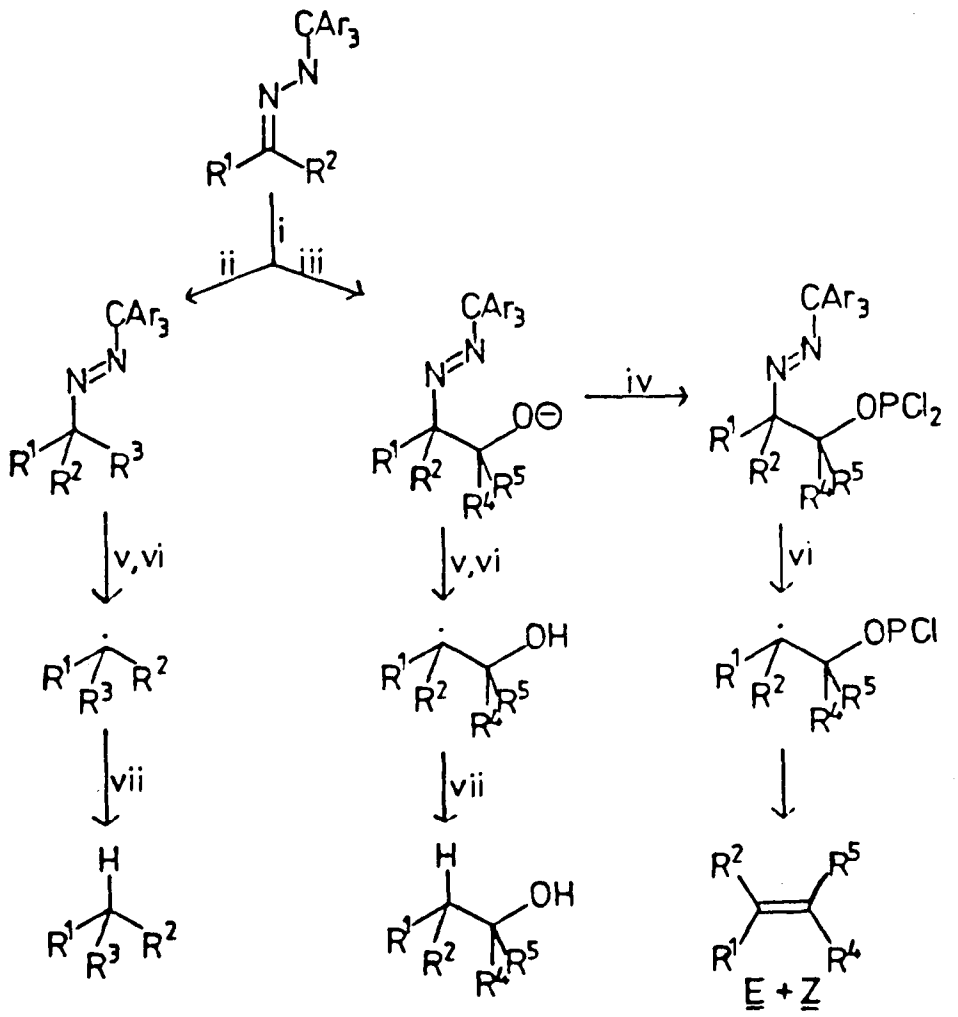
Nitrogen loss (paths C,D,E) could expect to be driven by the formation of dinitrogen gas, and could occur by either heterolytic (C,D) or homolytic (E) pathways.

Fragmentation of the type in path C has been reported for silylazo compounds,[57] where it is triggered by nucleophilic attack of methoxide on silicon. Attempts to induce this type of fragmentation with alkylazo compounds ($X=CR_3$) with β-leaving groups ($E=C(OCOCl)R^3R^4$) have been unsuccessful.[58]

Heterolytic fragmentation of the type in path D is analogous to the Shapiro[31,32] reaction, where the leaving group (X^-) is arylsulphinyl. We considered that such a leaving group would probably be incompatible with the requirements for C-alkylation of hydrazone anion.

Heterolytic fragmentation of azo compounds is a well-documented process.[59] We argued that, if a suitable X group was used for the hydrazones, radical fragmentation of the azoalkanes (XX) (path E) should be facile. Preliminary results[60] with tritylhydrazones ($X=CPh_3$) and diphenyl(4-pyridyl)methyl hydrazones ($X=CPh_2(4\text{-py})$) had shown that reaction with electrophiles gave C-adducts, and that the azo compounds (XX) decomposed around -20° to give radicals

that could be trapped by hydrogen atom sources to give alkanes or alcohols. (scheme 11) Conversion of the alkoxide (from addition to aldehydes or ketones) to a radical leaving group resulted in an olefin synthesis by reductive coupling of carbonyls. (scheme 11)



i n-BuLi ii R^3X iii R^4COR^5 iv Et_3N / PCl_3 / T>-20° v H^+ vi T>-20°, $-N_2$, $-{}^{\cdot}CAr_3$ vii EtSH

Scheme 11

Aims and Objectives

The aims at the start of this project were:

(1) to investigate further the reactions of t-butylhydrazones as acyl anion equivalents, particularly for Michael additions as a route to 4-keto functionalised

molecules.

(2) To improve the synthesis of alkanes from tritylhydrazones. Examination of the spectra of the resultant alkanes had revealed that, although undoubtedly present, the alkanes had not been formed cleanly and had not been purified completely. The possibility of trapping the radicals with reagents other than hydrogen atom sources, was also considered.

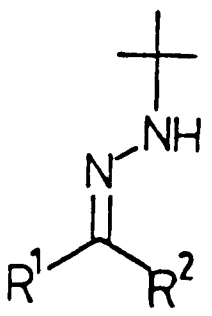
(3) To develop a hydrazone with an N-substituent such that a reaction on carbon could be followed by reductive cleavage to form amines by the equivalent of an α-amino anion.

CHAPTER 2

Reactions of t-Butylhydrazones

The Preparation of t-Butylhydrazones

t-Butylhydrazones (1) were prepared from t-butylhydrazine (aqueous solution, prepared from a solution of the hydrochloride and sodium hydroxide) and an aldehyde or ketone using an acid catalyst on a 0.5 mol scale. The hydrazones were isolated by distillation in good yields (table 1), mostly as a mixture of E and Z isomers. Though hydrolysis or auto-oxidation[61] are possible decomposition pathways it has been found that the hydrazones (1) are stable for about 18 months when stored at -18° under an inert atmosphere with light excluded. The hydrazones are thus convienient synthetic intermediates.



(1)

	R^1	R^2	yield/%	approx. isomer ratio
(1a)	Me	H	68	60:40
(1b)	Me	Me	72	-
(1c)	i-Pr	H	73	93: 7
(1d)	n-Bu	H	88	75:25
(1e)	$-(CH_2)_5-$		54	-
(1f)	$n-C_7H_{15}$	H	59	75:25
(1g)	Ph	H	85	>98: 2[a]

a only 1 isomer by ^1H n.m.r.

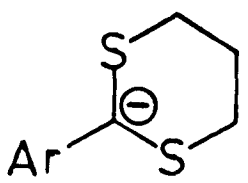
Table 1

The Synthesis of 4-Ketoesters and 4-Ketonitriles by Michael Additions of Acyl Anion Equivalents

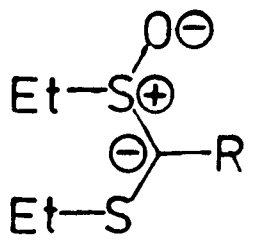
The Michael reaction of acyl anion equivalents is an important route to 1,4-difunctionalised molecules and thus has been subject to considerable investigation.

Seebach originally reported[62] that lithiodithanes add 1,2- rather than 1,4- to α,β-unsaturated carbonyl compounds. Later work,[63-65] notably that of Lucchetti and Krief,[63] has shown that lithiated dithioacetals and diselenoacetals can add to Michael acceptors in moderate yields under specially defined conditions (usually HMPT 1.1 equivalents in THF; or DME as solvent). More highly stabilised aryl dithiane anions (XXIII) have been shown to add 1,4- or 1,2- to enones depending upon the temperature.[66] Mukaiyama[67] has formed a cuprate from a dithiane anion which has given good yields of 1,4-adducts

with enones.



(XXIII)



(XXIV)

Schlessinger[68] has developed the use of the monosulphoxides of thioacetals (XXIV), the anions of which react with a wide variety of Michael acceptors to give good yields of 1,4-adducts without the use of HMPT.

Stetter has shown that cyanide ions[69-71] or thiazolium ions[72] catalyse the Michael addition of aldehydes to Michael acceptors. The yields are moderate to good, though cyanide ion works only for aromatic aldehydes. This method has the advantage of requiring neither masking nor deprotection steps. This mimics the use of thiamine in biological systems,[10] it is also similar to the benzoin condensation.[73] Related methods involve isolation of the intermediate cyanohydrin in a protected form[74,75] or the use of α-dialkylaminonitriles.[76] These methods are good for obtaining Michael adducts, though control of reaction conditions is important if 1,2-addition is to be avoided.

Lithiated vinyl ethers do not add 1,4- to Michael acceptors but they can be converted into cuprates (either simple or with a non-transferable alkynyl ligand) which give good yields of 1,4-adducts if the electrophiles are not β,β-disubstituted.[77,78] Vinylsilane reagents can also

be converted into cuprates that give 1,4-adducts with Michael acceptors.[79]

Other groups that have been used as acyl anion equivalents in reactions with Michael acceptors to give 1,4-adducts are nitriles,[80] nitro compounds[81] (methods for unmasking the carbonyl[22]), acyloins,[82] phenylthio-acetates,[83] glycine ester imines[84] (though the ketone was not unmasked), oxazolones[85] and acyl metal species derived from nickel carbonyl.[86]

Acyl radicals, derived from aldehydes, add 1,4- to α,β-unsaturated carbonyl compounds or α,β-unsaturated nitriles in variable yields.[87] In some cases excellent yields of 4-ketoesters, 4-ketonitriles or 1,4-diketones have been obtained and in these cases the method would seem to be of considerable value.

Other syntheses of 1,4-difunctionalised molecules have involved formation of different C-C bonds, but most involve some form of umpolung. Classical methods are reviewed in Rodd[88] and some more recent ones by Brown.[89] Important routes involve the use of bromoacetates[90,91] or nitroolefins[92] as enolonium ion equivalents with enolates; diazoacetates have been added to enol ethers,[93,94] the 4-ketoester is liberated by hydrolysis; and cyanide ion (a synthetic equivalent of a carboxyl anion) has been added 1,4- to enones.[95]

The Reactions of t-Butylhydrazone Anions with Michael Acceptors

The use of aldehyde t-butyl hydrazone anions as acyl anion equivalents has been demonstrated for the synthesis of α-hydroxyketones and ketones.[55,56] We decided to investigate the reactions of t-butylhydrazone anions with enoic esters as a means for the synthesis of 4-ketoesters, an important class of compound.

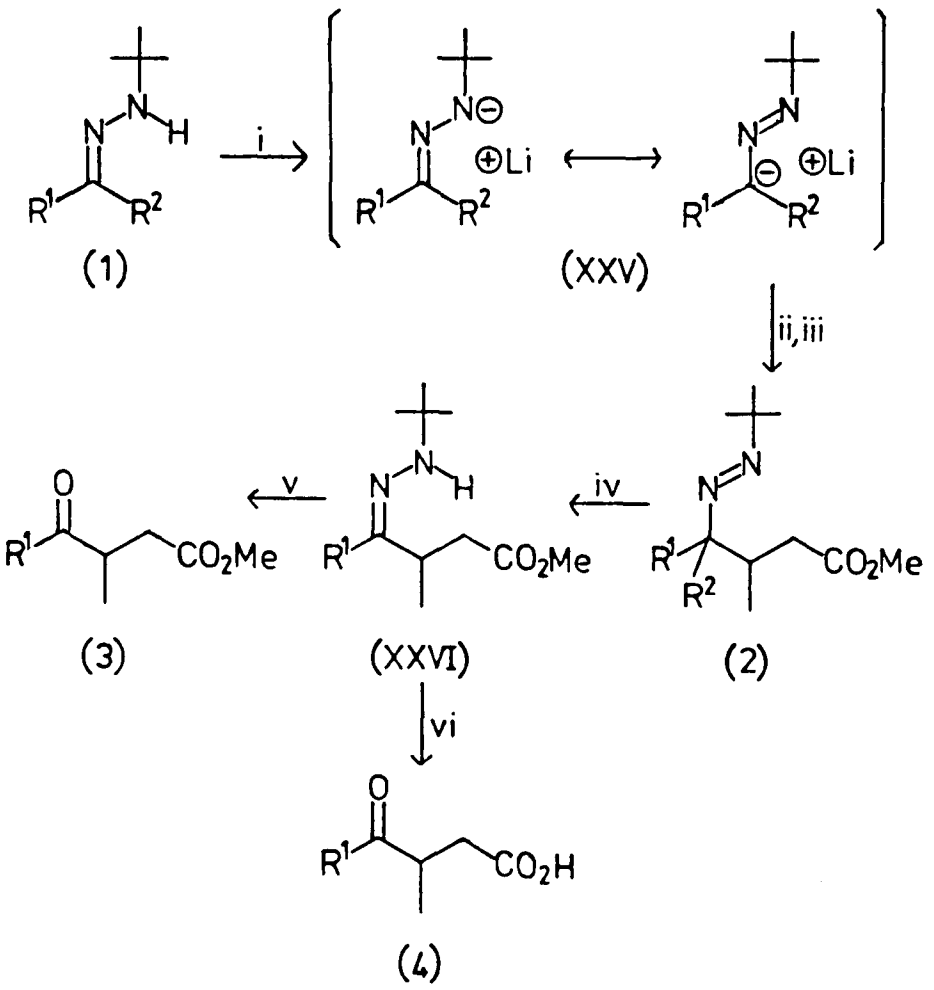
Initial reactions using aldehyde t-butylhydrazones (1), forming the anions with n-butyl lithium (1.1 eqivalents) at 0^{o} and adding either methyl acrylate or methyl crotonate at 0^{o} were unsuccessful; they gave complex mixtures as judged by t.l.c. and n.m.r.. The procedure was modified: the anion was cooled to -78^{o} before the ester was added but reactions with short (10 min.) or long (3h.) reaction periods, with quenching at -78^{o} or warming to room temperature before quenching were all unsuccessful with aldehyde t-butylhydrazones (1,R^2=H), with either methyl acrylate or methyl crotonate. Acetone t-butylhydrazone (1b), however, gave the azoester (2b) when methyl crotonate was added to the anion at -78^{o} and the reaction was quenched after 30 min. at -78^{o}. Cyclohexanone t-butylhydrazone (1e) similarly gave a moderate yield of the isolated azoester (2e) with methyl crotonate. Reaction of aldehyde t-butylhydrazones (1, R^2=H) using this procedure was unsuccessful until the amount of base was reduced to 0.95 equivalents. The azoesters (2) could then be isolated in good yields from both aldehyde and ketone t-

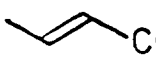
butylhydrazones (1). (table 2) The 4-azoesters (2, R^2=H) from aldehyde t-butylhydrazones were not normally isolated but treated in situ with TFA for 3-5h. to tautomerise them to the t-butylhydrazone form (XXVI). The hydrazones (XXVI) were then hydrolysed directly with aqueous oxalic acid, in a two-phase system with ether to the corresponding 4-ketoesters (3) in good yield. (scheme 12) (table 2)

57% Hydriodic acid was investigated in a two-phase system with ether as a "one pot" tautomerisation and hydrolysis of the azoesters (2, R^2=H). The 4-ketoesters (3) were isolated, but in lower yield than the two-step method. There were also other ketonic products visible by t.l.c. (as visualised by Brady's reagent). These could have been formed by acid catalysed aldol reactions.

The t-butylhydrazones (XXVIc) and (XXVIg) derived from isobutyraldehyde t-butylhydrazone (1c) and benzaldehyde t-butylhydrazone (1g) proved resistant to hydrolysis under the oxalic acid-water-ether conditions that had been used to hydrolyse the t-butylhydrazones of ketones,[55] α-hydroxyketones[55] and other 4-ketoesters (2a,d,f). This presumably results from the α,α' secondary centres making the transition state for a tetrahedral intermediate of higher energy because of steric crowding. More forcing methods of hydrolysis were investigated: titanium trichloride,[96] sodium periodate,[33] and 57% hydriodic acid were all unsuccessful, giving unhydrolysed starting hydrazone. The hydrazone moiety could be hydrolysed using

a solution of 1:1 2M hydrochloric acid: THF. Heating (2c) for 10h. at 50° gave the 4-ketoester (3c) in 13% yield plus the corresponding 4-ketoacid (4c), produced by hydrolysis of the methyl ester in addition to the hydrazone. 16h. at reflux proved sufficient to form the 4-ketoacids (4) only. (scheme 12) (table 2)



i n-BuLi (0.95 eq) ii  / -78° / 30min.

iii AcOH / -78° iv TFA / 3-5h. v $(COOH)_2$ / H_2O / Et_2O

vi 2M HCl / THF / reflux / 16h.

Scheme 12

hydrazone (1)			azoester (2)	ketoester (3)	ketoacid (4)
R^1	R^2		yield/%	yield/%	yield/%
Me	H	(1a)	-	58	-
Me	Me	(1b)	58	-	-
i-Pr	H	(1c)	54	-	47
n-Bu	H	(1d)	-	60	-
$-(CH_2)_5-$		(1e)	53	-	-
$n-C_7H_{15}$	H	(1f)	-	50	-
Ph	H	(1g)	68	-	47

yields based on n-BuLi

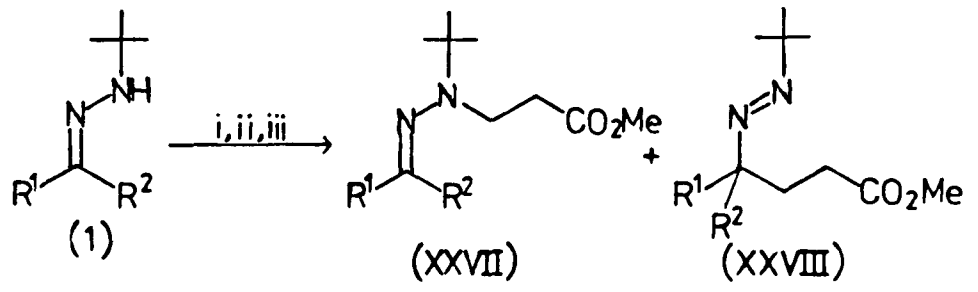
Table 2

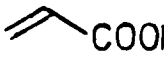
In an attempt to improve the yields of 4-ketoesters a reduced amount of methyl crotonate was added to an otherwise normal reaction. The ketoester (3d) was isolated in 76% yield based on the amount of crotonate added.

The method successfully used for addition of t-butylhydrazone anions to methyl crotonate was tried with methyl acrylate as electrophile, but from the n.m.r. spectrum the major product was that derived from Michael addition via nitrogen (XXVII). Only small amounts ($< 20\%$) of the C-adduct (XXVIII), (scheme 13) could be observed. The reaction was not considered sufficiently high yielding in 4-azoesters to merit further investigation. All other attempts to obtain Michael addition of t-butylhydrazone anions to methyl acrylate were unsuccessful.

Attempts to extend the reaction to other electrophiles were unsuccessful, methyl 3-methylbut-2-enoate (methyl β,β-

dimethylacrylate) gave no isolable product whilst acrylonitrile was polymerised under the reaction conditions.



i n-BuLi (0.95 eq) ii  / -78° iii AcOH / -78°

Scheme 13

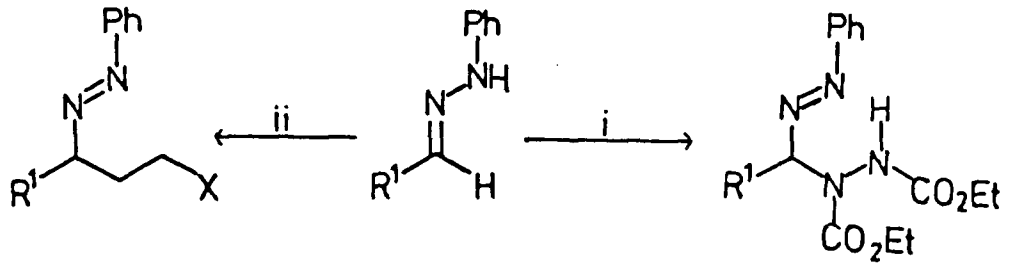
Snider[53] has prepared the cuprate of a lithiated phenylhydrazone and obtained reaction at carbon with acrylonitrile. Attempts to prepare a Gilman type cuprate ($R_2Cu\ Li$) from a t-butylhydrazone anion and cuprous iodide were all unsuccessful. Lipschutz[97] has pioneered the use of dialkylcopper cyanide reagents ($R_2CuCN\ Li_2$) and has claimed improved yields for many cuprate reactions. The anion of pentanal t-butylhydrazone (1d) was prepared and cooled to -78°, it was then added to 0.5 equivalents of cuprous cyanide according to the procedure of Lipschutz[97]. On warming a homogeneous solution was formed, this was recooled to -78°, when acrylonitrile was added. Quenching and workup after 2h. at ca -55° gave the 4-ketonitrile (7d) in 8% yield (based on cuprous cyanide, 4% based on starting hydrazone (1d)). No further work was attempted on t-butyl-hydrazone cuprates.

Conclusions

The anions of t-butylhydrazones have been shown to add 1,4- to methyl crotonate. The 4-azoesters (2, R^2=H) produced from the addition of aldehyde t-butylhydrazones (1, R^2=H) to methyl crotonate have been converted to 4-ketoesters (3) or 4-ketoacids (4). The method is unlikely to find widespread application as the overall yields are only moderate to good and strongly basic conditions are required.

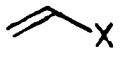
Ene reactions of t-Butylhydrazones

Ene reactions of phenylhydrazones have been reported. Aldehyde phenylhydrazones give ene adducts (XXIX) with diethylazodicarboxylate without heating.[98,99] (scheme 14) Under more vigo rous conditions ene reactions have been obtained with acrylates[53,54] (115-120°/30h. or 110°/48h.), acrylonitrile[53] (115-120°/30h.) and styrene.[54] (145°/72h.) (scheme 14) None of these adducts were exploited synthetically.[100]



(XXIX)

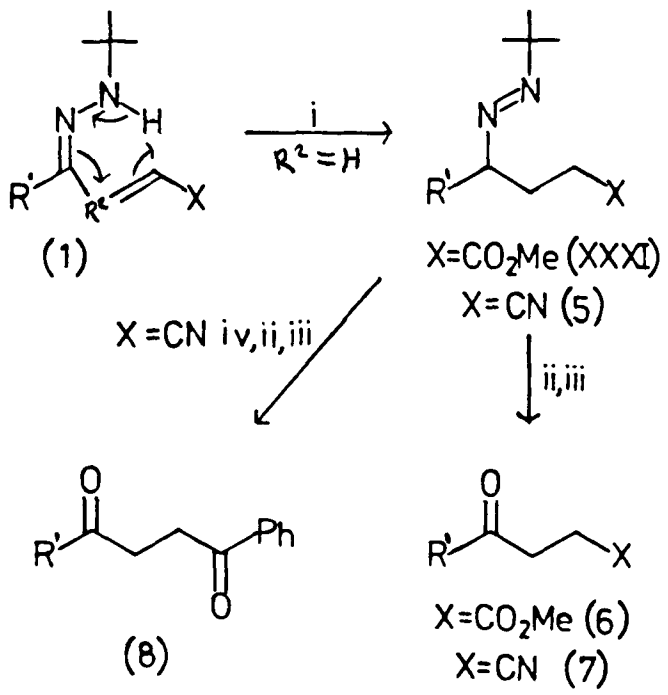
X= CO_2Me, CN, Ph

i $EtO_2CN{=}NCO_2Et$ ii  / Δ

Scheme 14

Alkylhydrazones have a greater electron density on nitrogen than phenylhydrazones; methylhydrazones have been shown[51,52] to add to methyl propiolate (a good enophile) to give N-adducts. We reasoned, however, that the steric factors that direct reaction of t-butylhydrazone anions to carbon could also retard Michael addition from nitrogen sufficiently to allow ene reactivity to compete.

Aldehyde t-butylhydrazones (1, R^2=H) were refluxed in xylene with methyl acrylate or acrylonitrile for 24h.. 4-t-Butylazoesters (XXXI) or 4-t-butylazonitriles (5) could be isolated from the reaction in good yields. Normally the azo compounds were not isolated but they were converted by tautomerisation (TFA) and hydrolysis (oxalic acid-water-ether) to the corresponding 4-ketoesters (6) or 4-ketonitriles (7) (scheme 15) mostly in excellent yields. (table 3) Benzaldehyde t-butylhydrazone (1g) gave no isolable adduucts with either methyl acrylate or acrylonitrile under these conditions.



i xylene or toluene / reflux / 24h. ii TFA / 3-5h.

iii $(COOH)_2$ / H_2O / Et_2O / 5-16h. iv PhMgBr / Et_2O

Scheme 15

hydrazone (1)	R^1	solvent	azonitrile (5) yield/%	ketoester (6) yield/%	ketonitrile (7) yield/%
(1a)	Me	t	-	80	-
(1c)	i-Pr	t	-	51	-
		x	-	77	18
(1d)	n-Bu	t	58	-	47
		x	-	74	55
(1f)	n-C_7H_{15}	t	-	-	51
		x	-	89	75

t toluene ; x xylene

Table 3

Cyclohexanone t-butylhydrazone (1e) and methyl acrylate gave less than 4% of the corresponding adduct. Methyl crotonate, methyl 3-methylbut-2-enoate, acrylic acid and methyl vinyl ketone were investigated as enophiles but in no case was any ene adduct isolated.

The use of toluene as solvent was investigated; for acetaldehyde t-butylhydrazone (1a) with methyl acrylate a good yield of 4-ketoester was isolated, but in general yields were lower than for reactions in xylene. (table 3)

The t-butylazo function is a protected carbonyl equivalent, provided tautomerisation to the t-butylhydrazone form is possible. To demonstrate this potential a "one pot" synthesis of 1,4-diketones was devised. The t-butylazonitrile (5a) from acetaldehyde t-butylhydrazone (1a) and acrylonitrile was prepared in toluene and added to a solution of excess phenyl magnesium

bromide in ether. After tautomerisation (TFA) and hydrolysis (oxalic acid-water-ether) the 1,4-diketone (8a) was isolated in 23% yield (from starting hydrazone). (scheme 5) Although relatively low-yielding this synthesis of 1,4-diketones utilises readily available starting materials and is extremely versatile in the nature of substituents that could be included.

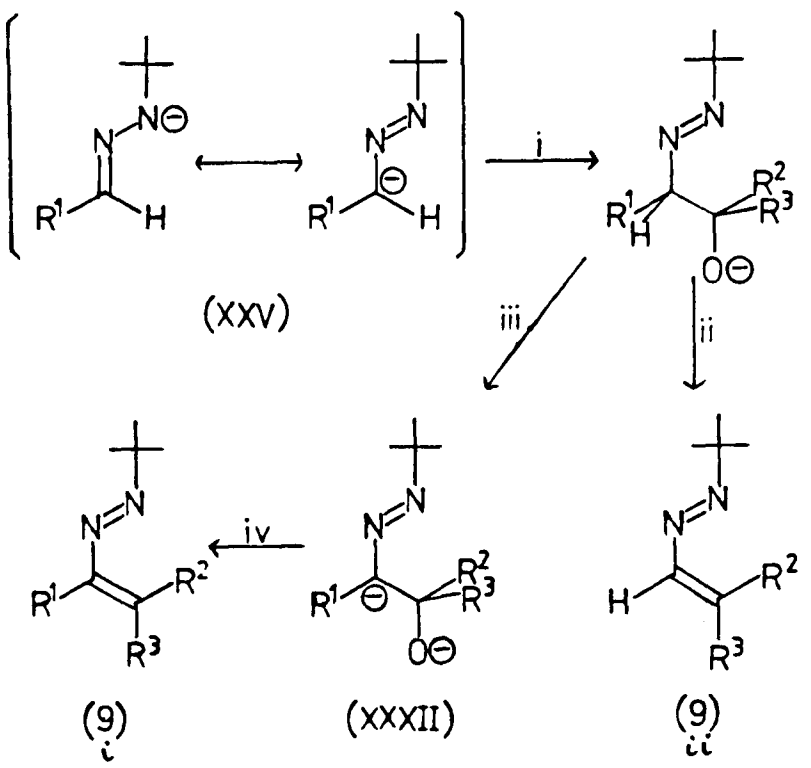
Conclusions

t-Butylhydrazones have been shown to undergo ene reactions with methyl acrylate and acrylonitrile on reflux in xylene. This is the first example of an ene reaction of an alkyl hydrazone. The reactions were clean and high-yielding and the ene adducts were converted by simple operations into synthetically useful 4-ketoesters and 4-ketonitriles, mostly in excellent overall yields. The disadvantages of the method are the use of relatively high temperatures (145^{o}) and the requirement of the enophile to be terminally unsubstituted. The advantages are that, unlike many acyl anion equivalents, strongly basic conditions are not required, experimentally the reactions are extremely simple and could easily be carried out on a large scale. The procedure thus represents an attractive synthetic method.

t-Butylazoalkenes

The synthesis of t-butylazoalkenes (9) by reaction of an azostabilised anion (XXV) with an aldehyde or ketone

followed by dehydr ative elimination has been established.[56] (scheme 16)



i R^2COR^3 ii $R^1=Me_3Si$ iii n-BuLi

iv Me_3SiCl, $(EtO)_2POCl$, $COCl_2$ or $SOCl_2$

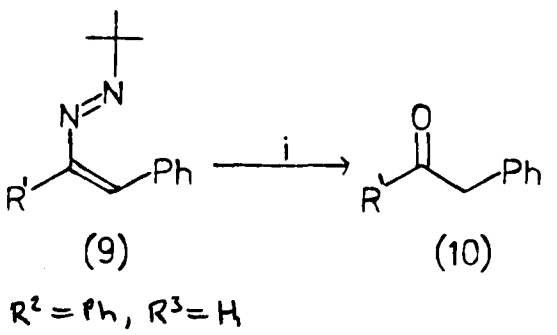
Scheme 16

The synthesis has been modified by using phosgene (solution in toluene) or thionyl chloride (the most conv enient reagent) to effect the final elimination from the dianion (XXXII). (scheme 16) This method was successful for the synthesis of (9c) from isobutyraldehyde t-butylhydrazone (1c) and benzaldehyde (65% with phosgene, 74% with thionyl chloride). The azoalkene (9c) was formed as a mixture of E,Z isomers which could be separated by chromatography, but the isolated isomers proved not to be configurationally stable. No azoalkene was isolated when isobutyraldehyde t-butylhydrazone (1c) and acetophenone were used under the same conditions. Reaction between

isobutyraldehyde t-butylhydrazone (1c) and butanal under these conditions gave an azoalkene (as judged by the appearance of a resonance at δ 5.55 (t) in the 60MHz n.m.r. spectrum of the crude material, assigned $CH_2C\underline{H}=C$) but this was too unstable to permit isolation.

Ene hydrazines have been reduced to saturated amines by zinc in acetic acid.[101] As part of an investigation of the reduction of N-N bonds to exemplify the use of hydrazone anions as α-amino anion equivalents (chapter 4) we decided to investigate the reduction of t-butylazoalkenes with zinc in acetic acid.

The azoalkenes (9) were heated to reflux with excess zinc in acetic acid, under an inert atmosphere. The t-butylazoalkenes conjugated with a phenyl group have an intense orange colour which was dissipated in ca 30s. on addition of zinc to the solution in acetic acid, demonstrating that initial reduction is extremely rapid. After 3h. reflux the reactions were worked up and ketonic products isolated. (scheme 17) (table 4)



(9) (10)

R^2 = Ph, R^3 = H

i Zn / AcOH / reflux / 3h.

Scheme 17

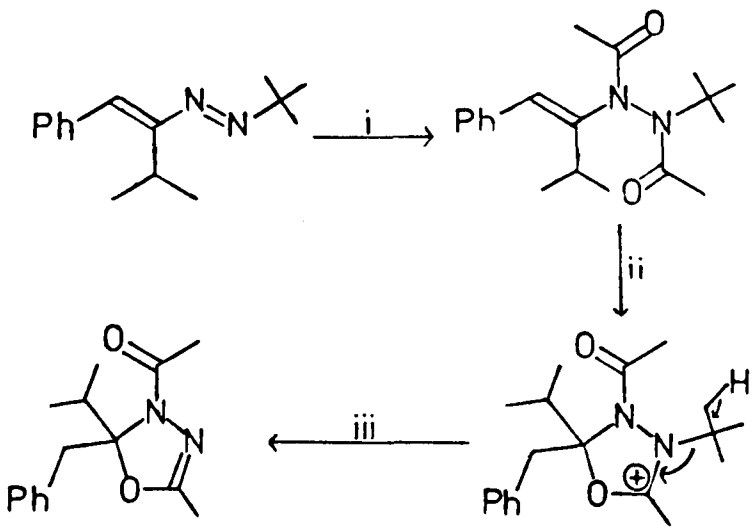
azoalkene (9)	R'	ketone (10) yield/%
a[102]	Me	55
c	i-Pr	49

Table 4

This was an unexpected result. It represents an overall homologation of benzaldehyde, though the overall yield is too low to be of practical value. We postulated that the reaction proceded via an imine as an intermediate (t-butylhydrazones are not hydrolysed under the reaction conditions) which was hydrolysed to the ketone by traces of water present in the reaction faster than it was reduced to the amine. In an attempt to produce a self-drying system a reaction was carried out in a mixture of acetic acid: acetic anhydride 1:1; under these conditions (9c) gave, as the major product, (23%) a compound that was neither the ketone (10c) nor the desired amine. The ^{1}H n.m.r. spectrum (fig. 1) contained an aromatic multiplet, a benzylic methylene as an AB quartet, an isolated isopropyl group with non-equivalent methyl groups, and two methyl singlets, one characteristic for an acetamide (δ 2.06), the other at higher field (δ 1.75). The ^{13}C n.m.r was consistent with a benzyl group and an isopropyl group with non-equivalent methyl groups. Two quartets, corresponding to the two methyl singlets in the ^{1}H spectrum were at δ 22.26 (acetamide) and δ 10.90. Four singlets were observed: one (δ 135.13) was assigned as the aromatic ipso carbon, one (δ 166.59) was assigned to an acetamide type structure. The

fig. 1

two remaining singlets were at δ 154.81 and δ 106.38. The signal at δ 154.81 was considered likely to be associated with the quartet at δ 10.90 and the higher field methyl singlet of the proton spectrum. δ 106.38 Was an unusual position for a carbon resonance, however for 2,2-dimethyl-1,3-dioxane the C-2 chemical shift was observed at δ 99.2,[103] whilst for acetaldehyde diethylacetal the C-2 resonance was observed at δ 99.5.[104] Many pyranose and furanose sugars have the hemiacetal carbon resonance in the range δ 92-107.[105] Infra-red spectroscopy indicated a band at 1659 cm^{-1}, characteristic of an amide. High resolution mass spectrometry gave a molecular formula of $C_{15}H_{20}N_2O_2$, indicating that the product has retained both nitrogen atoms of the starting azoalkene but lost the t-butyl group. A structure consistent with the data is (11c). A mechanism that could account for its formation is proposed in scheme 18.



(11c)

i $2e^-$ / $2Ac_2O$ ii H^+ iii $-H^+$

Scheme 18

Repetion of the reaction with (9a) gave a variety of products, including (10a), but no product analogous to (11c). These investigations were not pursued further as the prospects for succesful amine synthesis seemed poor.

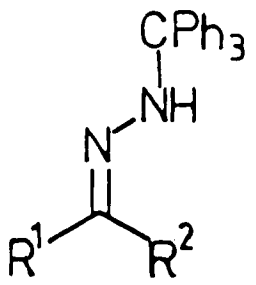
CHAPTER 3

Reactions of Tritylhydrazones

Preparation of Tritylhydrazine and Tritylhydrazones

Tritylhydrazine (20) was prepared by the alkylation of hydrazine with trityl chloride in refluxing THF. The hydrochloride salt was isolated in 90% yield after addition of methanolic hydrogen chloride and crystallisation. It was stored at 0^{o} and was stable for about 9 months.

Tritylhydrazones (21) were prepared from tritylhydrazine hydrochloride (20) and an aldehyde or ketone in the presence of sodium formate in a methanol-water solution under an inert atmosphere. The tritylhydrazones (21) prepared (table 5) were all crystalline[106] and were stable for about 6 weeks when stored at -18^{o} under an inert atmosphere.



(21)

Attempts to recrystallise the hydrazones resulted in decomposition and impurer products. The hydrazones were obtained in satisfactory purity by washing sequentially with water, methanol and finally petroleum, they were then

dried under high vacuum overnight.

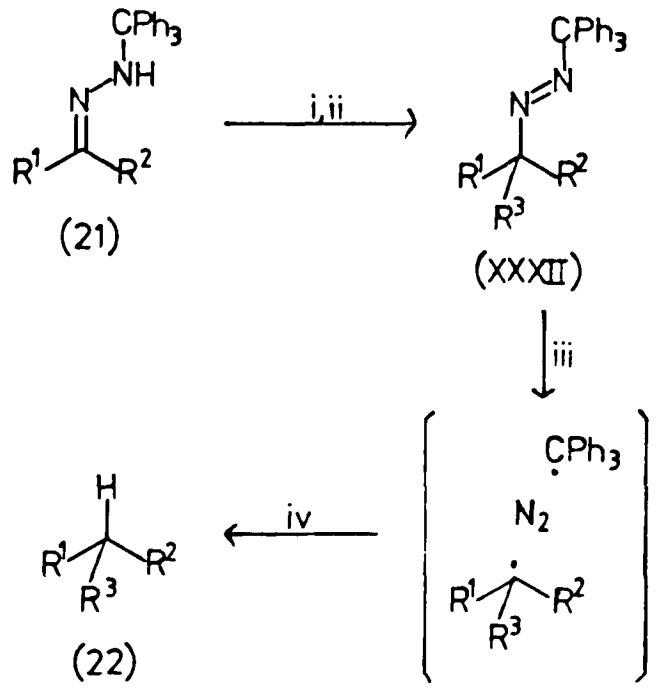
hydrazone	R^1	R^2	yield/%
21a	Me	H	56
21b	Me	Me	90
21d	n-Bu	H	77
21e	$-(CH_2)_5-$		89
21h	$-(CH_2)_4-$		79
21i	$-(CH_2)_{11}-$		87

Table 5

The Alkylations of Tritylhydrazones

Prior to the start of this project the alkylation of tritylhydrazones on carbon had been established[60] as an extension of earlier reported works on the C-alkylation of t-butylhydrazones.[55] The subsequent homolytic decomposition of the tritylazoalkane (XXXII) and the trapping of the resultant radical with ethanethiol to give alkanes (22) had been demonstrated.[60] (scheme 19) The homolysis of trityl-azoalkanes has literature precedent.[61]

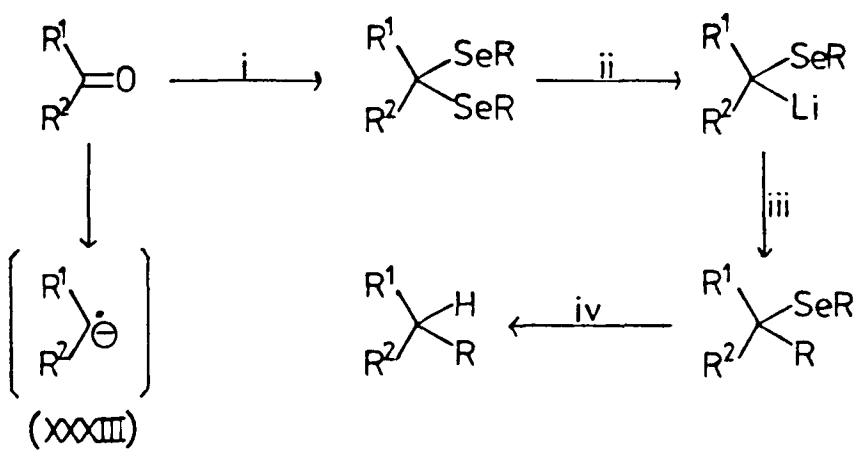
This process is analogous to the synthesis of alkanes from selenoacetals.[107,108] (scheme 20) In both cases the starting carbonyl is transformed into the equivalent of an anion and a radical. (XXXIII)



i $\underline{n}$-BuLi / -40^{o} ii R^3X / -30^{o} iii $--20^{o}$

iv EtSH

Scheme 19



i 2RSeH / $ZnCl_2$ (cat.) ii $\underline{n}$-BuLi / -78^{o}

iii R^3X / -78^{o}-25^{o} iv Li / $EtNH_2$ or Ra-Ni/H_2 or Ph_3SnH[108]

Scheme 20

Close examination of the spectra of the alkanes (22) produced by the alkylation of tritylhydrazones (21) by Baldwin et al[60] revealed the presence of impurities (as

indicated by e.g. the ratio of the integral of $C\underline{H}_3$ to $C\underline{H}_2$ in ^1H n.m.r., additional peaks in ^{13}C n.m.r. e.g. δ 29.74 for heptylcyclohexane produced from (21e) and 1-iodoheptane). These peaks arose from additional alkanes produced as by-products in the reactions, e.g. Wurtz type couplings of alkyl halide with butyl lithium, or lithium exchange followed by Wurtz coupling of the alkyl halide. This latter product was confirmed by the synthesis of tetradecane, (22ad) from acetaldehyde tritylhydrazone (21a) and 1-iodododecane. ^{13}C N.m.r. of the authentic tetradecane indicated an intense peak at δ 29.74 (unresolved methylene $\underline{C}5$-$\underline{C}9$), identical to that of the by-product present in the heptylcyclohexane. Careful examination of the mass spectra of the alkanes also revealed the presence of the low levels of undesired coupling products, e.g. m/e 198 ($C_{14}H_{30}^+$) in the mass spectrum of heptylcyclohexane. As the alkane by-products were inseparable by column or plate chromatography, unless aromatic groups were present, it was decided that further work to achieve a cleaner alkane synthesis was required.

Initially methyl lithium was used as the base in place of n-butyl lithium. This had the advantage of increasing the volatility of the by-products from the coupling of the alkyl halide and the base, but coupling of the alkyl halide with itself remained a problem. Use of a deficiency of base (0.95 equivalents) did not overcome the problem of the coupling of the alkyl halide with itself. Gas-liquid chromatography using a silicone oil stationary phase to

separate alkanes was used to analyse the alkanes obtained by plate chromatography. Integration of the g.c. trace gave the yield of the desired alkane as a percentage of the isolated alkanes.

Changing to use of LDA as base gave alkanes free from coupling by-products (single products by g.c.) however the yields were significantly lower than when alkyl lithium reagents were used as base. (table 6)

hydrazone	R^1	R^2	base	R^3-X	product	yield/%
21a	Me	H	LDA	n-$C_{12}H_{25}$-I	22ad	27
21b	Me	Me	LDA	n-$C_{12}H_{25}$-I	22bd	38
21d	n-Bu	H	LDA	n-$C_{12}H_{25}$-I	22dd	46
21e	-$(CH_2)_5$-		MeLi	$PhCH_2$-Br	22ea	69
21e	-$(CH_2)_5$-		MeLi	n-Bu-I	22eb	39*
21e	-$(CH_2)_5$-		MeLi	n-C_7H_{15}-I	22ec	69*
21h	-$(CH_2)_4$-		LDA	n-$C_{12}H_{25}$-I	22hd	27
21i	-$(CH_2)_{11}$-		MeLi	$PhCH_2$-Br	22ia	45
21i	-$(CH_2)_{11}$-		MeLi	n-Bu-I	22ib	51*

* yield based on integration of g.c. trace of isolated alkanes

Table 6

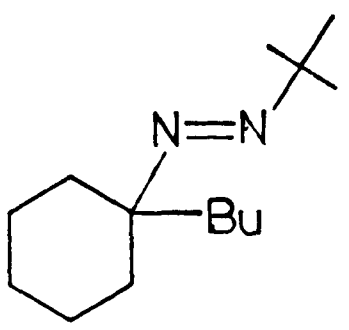
Other modifications to the original procedure included increasing the reaction time to 3h. at -30° before quenching with acetic acid and ethanethiol, this was to allow longer for the alkylation to occur as the reaction is slow at low temperatures. Reaction times of longer than 3h. were not investigated because of the experimental

inconv.enience.

Alkyl bromides and alkyl tosylates were investigated as electrophiles in place of alkyl iodides, but in both cases the yields of isolated alkanes were very low (<10%).

A practical modification was that rather than removing excess ethanethiol by distillation (unpleasant rather than difficult) a base wash, using sodium hydroxide solution, was substituted removing the thiol as the sodium thiolate.

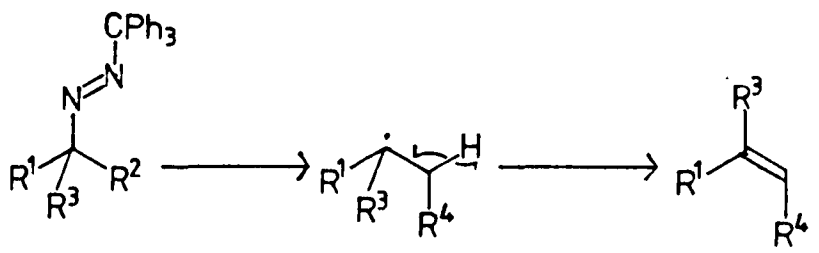
Cyclohexanone t-butylhydrazone (1e) was alkylated under the same conditions as the tritylhydrazones (21), but without the addition of ethanethiol. The t-butylazoalkane (12e) was isolated in 74% yield. This result showed that the radical decomposition and trapping of the tritylazoalkanes (XXXII) can be extremely efficient (the alkanes (22ea), (22eb) and (22ec) were isolated in 39-69% yield).



(12e)

The alkanes produced in these reactions were usually contaminated by small amounts of olefins. These were probably produced by hydrogen atom loss from the intermediate radical (XXXIV) rather than trapping by ethanethiol. (scheme 21) These olefinic by-products were visible in the 300 MHz n.m.r. spectra as small multiplets

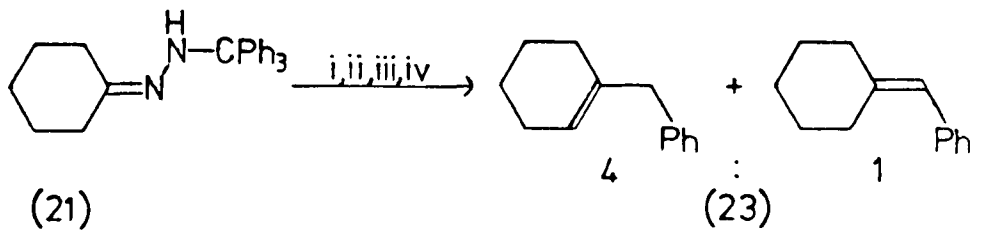
in the range δ 5.0-6.7. The olefins were easily removed by bromination immediately prior to the final chromatographic purification.



(XXXII) (XXXIV)

Scheme 21

To investigate this reaction and to see if there was any potential for development into an olefin synthesis cyclohexanone tritylhydrazone was benzylated and quenched with acetic acid as normal, but allowed to warm to room temperature without the addition of ethanethiol. The two expected olefins (23) were isolated by chromatography, but in only 9% combined yield. The product possesed a ratio of 4:1 unconjugated to conjugated olefin, based on the integration of the ^{1}H n.m.r. spectrum. (scheme 22)



(21) 4 : 1 (23)

i n-BuLi / -40° ii BnBr / -30° / 3h.

iii AcOH iv → R.T.

Scheme 22

Thus the ability of the radical (XXXIV) to give olefins under the reaction conditions was demonstrated but it had no practical utility owing to the low yield of olefin obtained.

The radicals produced in the decomposition of the tritylazoalkanes (XXXII) should provide a means for further reaction at the radical centre. This potentially could provide a route to quaternary carbon centres. Studies using bromine in a large excess in place of ethanethiol were without success and no alkyl bromides were isolated. Following this failure the use of radical traps in stoichiometric amounts was not investigated. The disadvantages of the decomposition of tritylazoalkanes for synthetic applications of radicals are that the radicals are rapidly generated in high effective concentration, rather than discretely in chain carrying processes, as in many recently published methods,[5,6] and that the radicals are generated in the same medium in which the alkylation was carried out.

An alternative synthesis of alkanes by hydrazone methodology has subsequently been developed.[106]

Conclusions

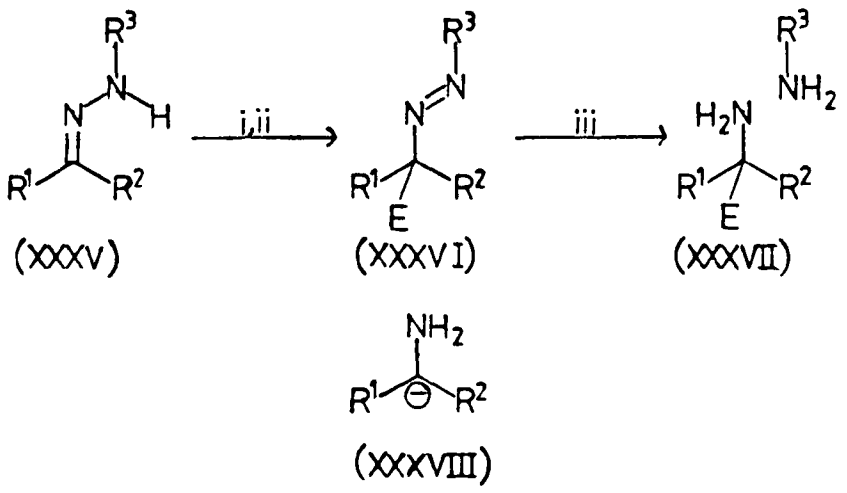
The synthesis of alkanes (22) from tritylhydrazones (21) has been improved from the initial procedure[60] and the method now constitutes a reliable method for the reductive alkylation of carbonyl compounds to alkanes.

CHAPTER 4

Reactions of Secondary Alkyl Hydrazones

Rationale

The third objective of the project was to develop a synthesis of amines via C-alkylation of hydrazones followed by reductive cleavage of the N=N double bond of the resultant azoalkane. (scheme 23) This would represent the use of hydrazone anions as the synthetic equivalents of α-amino carbanions of primary amines. (XXXVIII)



(XXXV) (XXXVI) (XXXVII) (XXXVIII)

i B^- ii E^+ iii reduction

Scheme 23

To achieve this objective the group R^3 of the hydrazone (XXXV) needed to be sufficiently sterically bulky to direct reaction to carbon. The same group R^3 on the azoalkane (XXXVI) must not prevent reduction of the N=N bond. The t-butylazoalkanes (12) produced by alkylation of t-butylhydrazones (1) proved resistant to reductive cleavage, even under forcing conditions.[109] Phenylazo compounds, in contrast were readily cleaved by reductive methods,[100]

however attempted reactions of the phenylazoanions with alkyl halides or aldehydes and ketones did not lead to C-adducts.[36]

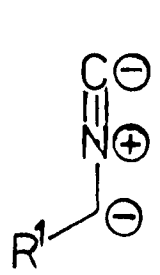
We chose to vary the secondary alkyl groups R^3, to investigate C-reaction of their anions. If azo compounds could be formed in good yield we proposed to investigate routes by which reductive cleavage to amines could be achieved. The reductive cleavage to amines of nitrogen-nitrogen bonds with secondary alkyl substituents has precedent.[110-114]

α-Primary Amino Anion Equivalents

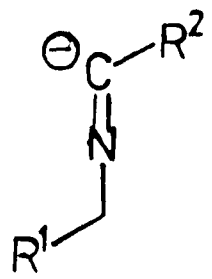
The development of methods providing synthetic equivalents of α-amino anions has been persued actively since Seebach and Enders[115] first introduced N-nitrosamines in 1972. The field has been reviewed extensively.[7,19-21] Of the many methods that have been published, however, relatively few are applicable to primary amines, and those that have been reported are of limited scope. (Methods for the synthesis of α-amino acids *via* essentially functionalised enolate equivalents are not considered here.[116])

Metallated isocyanides (XXXIX)[117,118] can act as α-amino anion equivalents but their usefulness is limited by the susceptibility of the isocyanide to nucleophilic attack to form a metallated aldimine (XL). Isocyanides that are less acidic than methylisocyanide (including all saturated

isocyanides other than cyclopropyl and cyclobutyl) can not be metallated.[118] This restricts their use to activated systems.



(XXXIX)

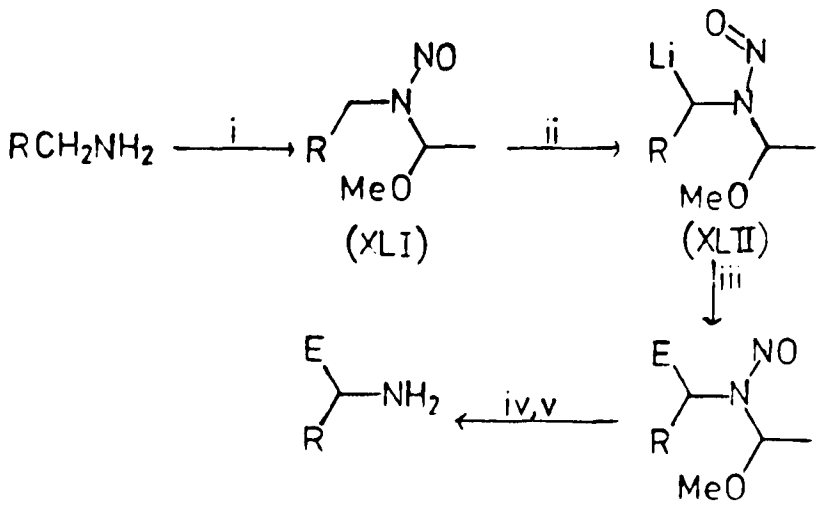


(XL)

N-Nitrosamines[115] are an important class of secondary α-amino anion equivalents, Saavedra[119] has developed a modification of the nitrosamine method to extend it to primary amines. The amine is initially converted to an aminoalkylether which is then N-nitrosated to (XLI) and finally metallated. (scheme 24) The metallated nitrosamines (XLII) react well with both alkyl halides and aldehydes and ketones.

The well-known[120] carcinogeneity of N-nitrosamines detracts from the attractiveness of this methodology, and it has yet to be applied synthetically.

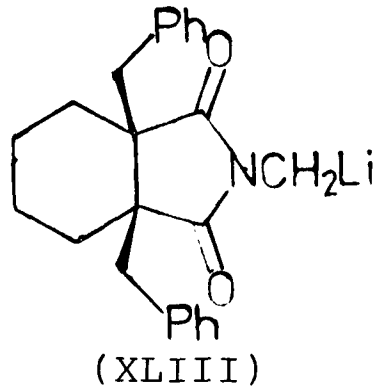
The anions derived from the amides of secondary amines where the carbonyl group is hindered to nucleophilic attack, and enolisation is not possible, have been widely studied as synthetic equivalents for α-amino anions.[21] The tetraalkyl succinimide (XLIII) has been investigated as a methylamine C-anion equivalent.[121] The yields of C-adducts are variable but always include around 20% of the dimer (XLIV).



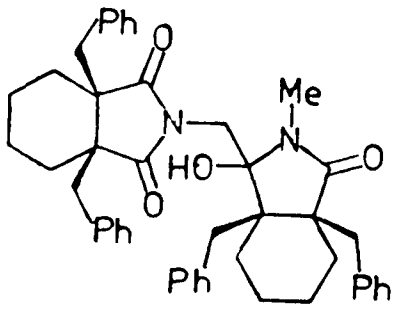
i CH_3CHO / MeOH / HONO ii LDA iii E^+

iv EtOCOCl / H_2O / acetone v 6M HCl / reflux

Scheme 24

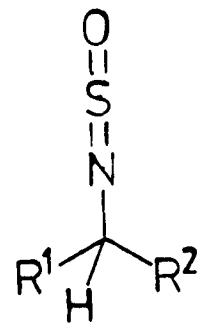


(XLIII)

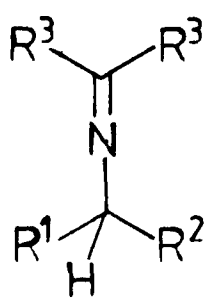


(XLIV)

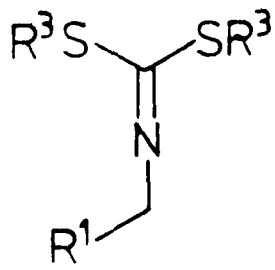
Sulphinylamines (XLV) give anions with potassium t-butoxide that react with allyl halides or enones, but not alkyl halides, to give, after work up, amines in moderate yields.[122]



(XLV)



(XLVI)

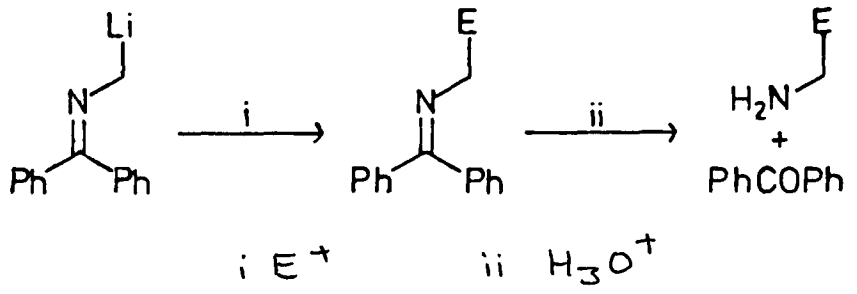


(XLVII)

The anions of imines (XLVI) have been investigated as potential α-amino anion equivalents. The anions of benzophenone methylimine[123-125] and more highly activated imines[126] have been successfully alkylated, they also react with aldehydes and ketones on the α-carbon. Liberation of the homologated amine is facile. (scheme 25)

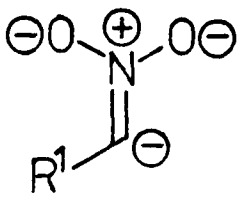
Iminodithiocarbonates (XLVII) are related to imines structurally. When the α-protons are activated the anions have been successfully formed with potassium t-butoxide and

alkylated.[127,128] Unactivated systems were not α-deprotonated.

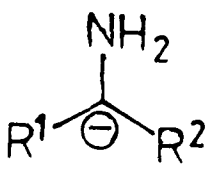


Scheme 25

Nitro compounds have long been used as α-amino anion equivalents. The recent discovery that dianions can be generated from nitro compounds with 2 equivalents of n-butyl lithium and that these dianions (XLVIII) react with alkyl halides on carbon[22] (unlike the monoanions) has considerably extended their value.



(XLVIII)



(XLIX)

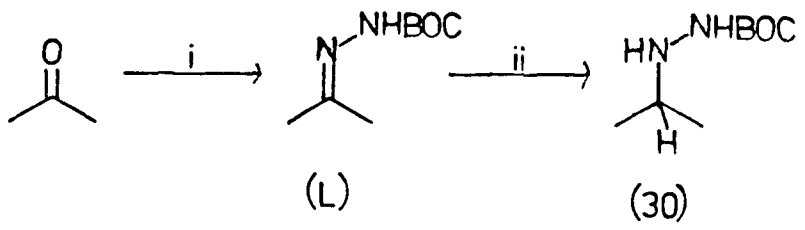
Consideration of the published methods reveals that there is no general synthetic equivalent of an α-amino carbanion where the anion is generated at an unactivated secondary centre (XLIX). The dianions of nitro compounds (XLVIII) are the only general synthetic equivalents of α-amino anions generated at an unactivated primary carbon centre. The potential for the development of novel α-amino anion methodology based on hydrazone chemistry was thus apparent.

Synthesis of Secondary Alkyl Hydrazines and their Hydrazones, Reactions of the Anions of the Hydrazones

A: Isopropylhydrazones

Initially we chose to prepare isopropylhydrazones (31) as they represent they the simplest second ary system. The most commonly used method for the preparation of isopropyl-hydrazine involved direct alkylation of hydrazine with isopropyl bromide.[129] As an attempt to prepare isopropyl-hydrazine using this method was very low-yielding we decided that a t-butylcarbazate approach[130] would be more attractive as it potentially avoided the ne cessity of isolating isopropylhydrazine.

Acetone BOC hydrazone (L) was prepared[131] and the crude product catalytically hydrogenated to give BOC isopropyl-hydrazine (30) (scheme 26) in 91% yield.



(L) (30)

i $BOCNHNH_2$ ii H_2 / Pt-C / EtOH

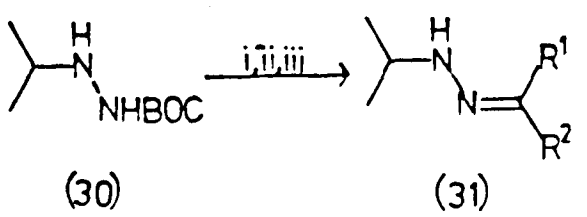
Scheme 26

The synthesis could be carried out on large scale (the limitation being principally hydrogenator capacity) and gave a crystalline protected hydrazine.

Deprotection of the BOC isopropylhydrazine (30) was carried out by stirring with a solution of hydrogen

chloride in methanol until gas evolution ceased, usually for about 2h.. Concentration gave a solid, whose 60MHz n.m.r. spectrum (CD_3OD) indicated an isopropyl moiety, but no singlet for t-butoxy, consistent with isopropylhydrazine hydrochloride.

Preparation of isopropylhydrazones (31) from the crude isopropylhydrazine hydrochloride was achieved by a modification of the procedure used for the preparation of t-butylhydrazones (1). The crude product from deprotection and concentration was dissolved in water (4ml/mmol) and the pH adjusted to 10-11 by addition of solid sodium hydroxide. Aldehyde or ketone (1.1 equivalents) was added and the reaction stirred under an inert atmosphere for 2h.. Ether extraction gave the hydrazone which was purified by distillation. This method gave only poor yields of isopropylhydrazones (31) but sufficient material could be prepared to investigate the reactions of their anions. (scheme 27) (table 7)



(30) (31)

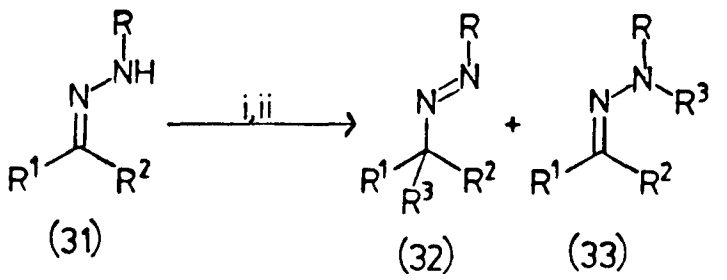
i MeOH / HCl ii NaOH / H_2O iii R^1COR^2

Scheme 27

	R^1	R^2	yield/%
(31b)	Me	Me	19
(31g)	Ph	H	18

Table 7

Alkylation studies of the isopropylhydrazones (31) were performed by the method developed for the synthesis of ketones from t-butylhydrazones.[55,56,132] Thus the anions from isopropylhydrazones were formed at 0° then cooled to -78° when an alkyl halide was added. The reaction was allowed to warm slowly to room temperature and then to stir overnight. Examination of the 300MHz n.m.r. spectra of the crude products from the reactions gave the ratios of C:N alkylation. (scheme 28, R=isopropyl) (table 8)



i n-BuLi / 0° ii R^3X / -78° → 0°

Scheme 28

hydrazone	R^1	R^2	R^3X	approx. ratio C:N
(31b)	Me	Me	BnBr	1:>2
(31g)	Ph	H	BnBr	1:1
(31g)	Ph	H	n-BuI	1:1

Table 8

The ratios were based on the integration of characteristic resonances for each compound. The resonances

were assigned with reference to known compounds: for N-benzylhydrazones (33) benzylamine (δ 3.88, s, $PhC\underline{H}_2NH_2$[133]) and benzaldehyde isopropylhydrazone (31a) (δ 3.60, 3.93, 2x septet, $Me_2C\underline{H}N$ of two isomers) were used as references. For C-alkylated compounds the reference was 1-phenyl-2-t-butylazopropane (LI)[56] (δ 3.68-3.75, multiplet, $PhCH_2C\underline{H}$). Thus for the reaction of the anion of acetone isopropylhydrazone with benzyl bromide (fig 2) the ratio was based upon the integrals of the singlet at δ 3.80 ($N\text{-}C\underline{H}_2Ph$) to those of the septet at δ 3.66 ($Me_2C\underline{H}N$) and the singlet at δ 2.93 ($C\text{-}C\underline{H}Ph$). For benzaldehyde isopropylhydrazone (31g) anion with benzyl bromide the integrals of the singlet at δ 4.40 ($N\text{-}C\underline{H}_2Ph$) to the multiplet (dd) at δ 4.71 ($PhC\underline{H}CH_2Ph$) and the multiplet (AB q of d) centred at δ 3.38 ($PhCHC\underline{H}_2Ph$) were used. For the products of the reaction between benzaldehyde isopropylhydrazone (31g) anion and 1-iodobutane the resonances on which the ratio was based were those at δ 4.39 (ca t, $PhC\underline{H}CH_2Pr$) against δ 3.66 (t, $NC\underline{H}_2Pr$) and δ 3.69 (septet, $NC\underline{H}Me_2$)

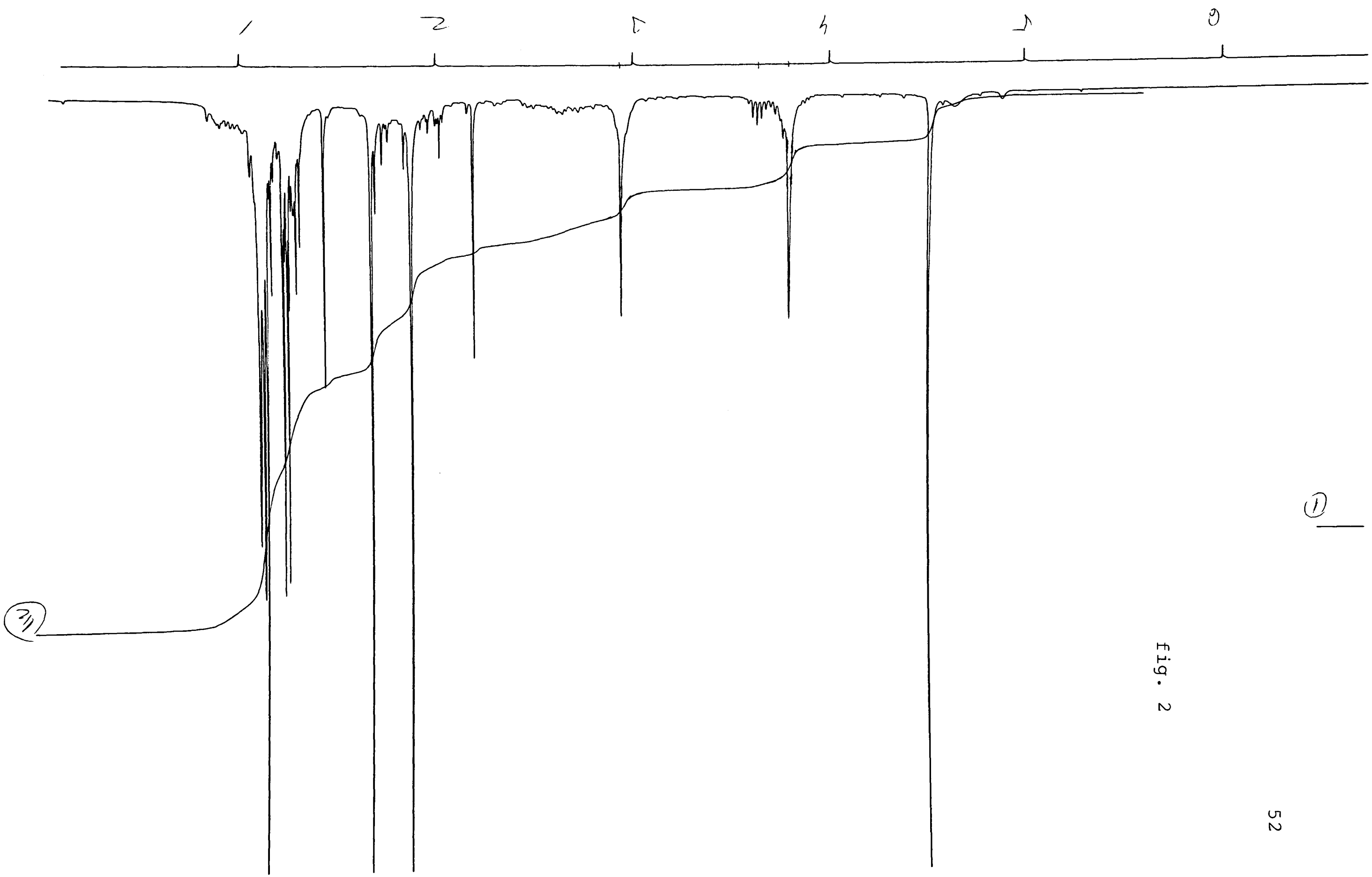
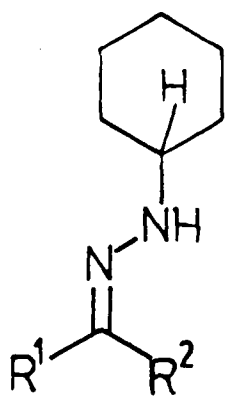


fig. 2

B:Cyclohexylhydrazones

To extend the investigation we decided to prepare cyclohexylhydrazones (41). BOC Cyclohexylhydrazine[130] (40) was prepared in 97% yield analogously to BOC isopropylhydrazine (30). Cyclohexylhydrazones (41) were prepared by the same method as isopropylhydrazones (31) but were isolated in better yield. (table 9)



(41)

	R^1	R^2	yield/%
(41a)	Me	H	46
(41b)	Me	Me	23
(41g)	n-Pr	H	51*
(41j)	Ph	H	70

* not completely pure

Table 9

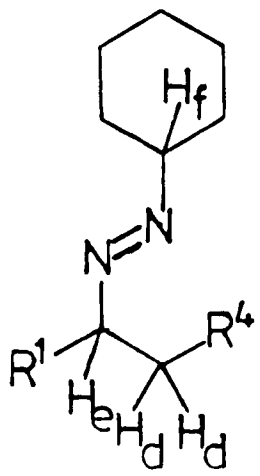
The preparation of acetaldehyde cyclohexylhydrazone (41a) by the standard procedure proved troublesome as one preparation gave 46% whilst two others gave only tars. A modified procedure for the preparation of hydrazones was investigated in an attempt to overcome this problem. The crude hydrochloride from the deprotection of the BOC cyclohexylhydrazine (40) was dissolved in methanol:

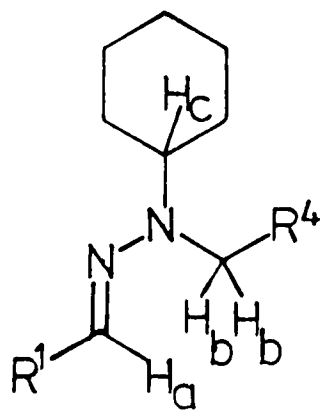
dichloromethane (1:1) and excess triethylamine was added to liberate the free hydrazine. The aldehyde or ketone was added to this solution and the solution stirred for 90min.. Concentration gave the hydrazone and triethylamine hydrochloride, which were separated between dichloromethane and water. The hydrazone was isolated by distillation. Using this procedure acetaldehyde cyclohexylhydrazone (41a) was isolated in 53% yield.

Alkylations of the cyclohexylhydrazones (41) were carried out by the procedure used for isopropylhydrazones (31). The C:N ratios were studied by examination of the n.m.r. spectra. (scheme 28, R=cyclohexyl) (table 10) (table 11)

	hydrazone		alkyl halide		approx. ratio
	R^1	R^2	R^3	X	C:N
(41a)	Me	H	Bn	Br	1:6
(41a)	Me	H	n-C_7H_{15}	I	1:2
(41g)	Ph	H	Bn	Br	2:1
(41g)	Ph	H	n-Bu	I	>2:1
(41j)	n-Pr	H	Bn	Br	1:7
(41j)	n-Pr	H	n-Bu	I	1:10

Table 10





Positions of Characteristic Resonances of

Alkylated Cyclohexylhydrazones

(41)	R^3	X	a	b	c	d	e	f
a	Bn	Br	6.41q	4.15s	3.29m	3.02*	-	-
a	$\underline{n}$-C_7H_{15}	I	6.67q	2.88t	3.03m	-	3.32m	3.28m
g	Bn	Br	-	4.45s	-	3.35*	4.69x	-
g	$\underline{n}$-Bu	I	-	-	-	-	4.34t	3.37m
j	Bn	Br	6.39t	4.15s	3.29m	3.02*	-	-
j	$\underline{n}$-Bu	I	6.65t	2.90t	3.06m	-	3.30m	3.39m

* = ABq of d x = dd - = obscured or not present

Table 11

The C or N reactivity of the hydrazone anions from (31) or (41) could be dependant on the nature of the electrophile. To investigate this possibility we decided to carry out a reaction with benzaldehyde as the electrophile. The azoalcohols derived from t-butylhydrazones and aldehydes or ketones were found[56] to be unstable so rather than try to isolate an azoalcohol we decided to use an aldehyde cyclohexylhydrazone and follow the procedure for the α-hydroxyketone preparation from t-butylhydrazones.[56] (scheme 9)

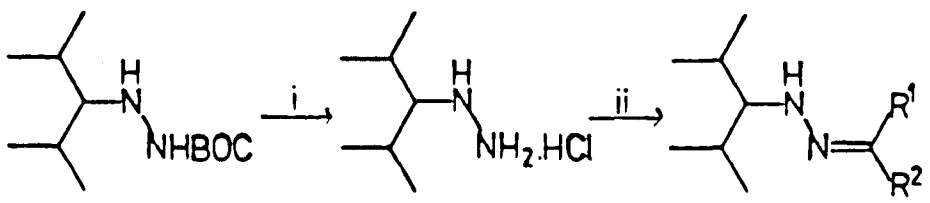
Acetaldehyde cyclohexylhydrazone (41a) was deprotonated with n-butyl lithium, and benzaldehyde was added. A second equivalent of n-butyl lithium was added to deprotonate any azoalkoxide formed. The reaction was quenched with water. Examination by 300MHz n.m.r. spectroscopy was inconclusive as to whether any α-hydroxyhydrazone was present so the crude product was subjected to oxalic acid hydrolysis. No α-hydroxyketone (56a) was isolated. We concluded, therefore, that C reaction was negligible. (scheme 31, path b, $R^3,R^4=(CH_2)_5$)

The experiments with isopropyl- (31) and cyclohexyl-hydrazones (41) show that a simple secondary centre does not hinder the nitrogen atom of the hydrazone anion sufficiently to direct extensive reaction to carbon. The difference between the C:N alkylation ratios obtained for aliphatic aldehyde and benzaldehyde hydrazones was noticeable. The higher degree of C-alkylation with the benzaldehyde hydrazones is probab l y related to the well-

known α-kinetic alkylation of conjugated enolates.[134] The results suggested that systems with slightly more steric hind rance might give synthetically useful levels of C-alkylation.

C: 2,4-Dimethylpent-3-ylhydrazones

2,4-dimethylpent-3-yl (DMP) hydrazones (51) were chosen as the next system to be investigated. This system has a secondary alkyl centre flanked by two α-secondary centres. The greater steric hind rance of such a system was demonstrated as soon as we attempted to prepare BOC DMP hydrazine (50). Thus stirring 2,4-dimethylpentan-3-one in dichloromethane with t-butylcarbazate and acetic acid catalyst did not lead to formation of the BOC hydrazone of 2,4-dimethylpentan-3-one, in contrast to the preparation of the BOC hydrazone of cyclohexanone. The BOC hydrazone of 2,4-dimethylpentan-3-one was prepared successfully, however, by carrying out the reaction in refluxing ethanol for 21h.. The crude BOC hydrazone was not isolated but immediately hydrogenated to give BOC DMP hydrazine (50) (ca 90%) as an impure oil. The crude material was used for the preparation of DMP hydrazones (51) which were prepared by the non-aqueous method developed for acetaldehyde cyclohexylhydrazone (41a). (scheme 29) (table 12)



(50) (51)

i HCl / MeOH ii R^1COR^2 / MeOH / CH_2Cl_2 / Et_3N

Scheme 29

hydrazone	R^1	R^2	yield/%[a]
(51a)	Me	H	40
(51b)	Me	Me	44
(51k)	Et	H	42
(51l)	Bn	Me	48*

a based on crude BOC DMP hydrazine

* slightly impure

Table 12

Alkylations of the DMP hydrazones were carried out by the procedure used for isopropyl- (31) and cyclohexyl-hydrazones (41). Examination of the crude 300MHz n.m.r. spectra showed no evidence for any N-alkylated products, though the C-alkylated products were clearly visible. (fig. 3) The DMP azoalkanes (52) were isolated by chromatography in good yields. (scheme 31, path a, R^3=R^4=i-Pr) (table 13)

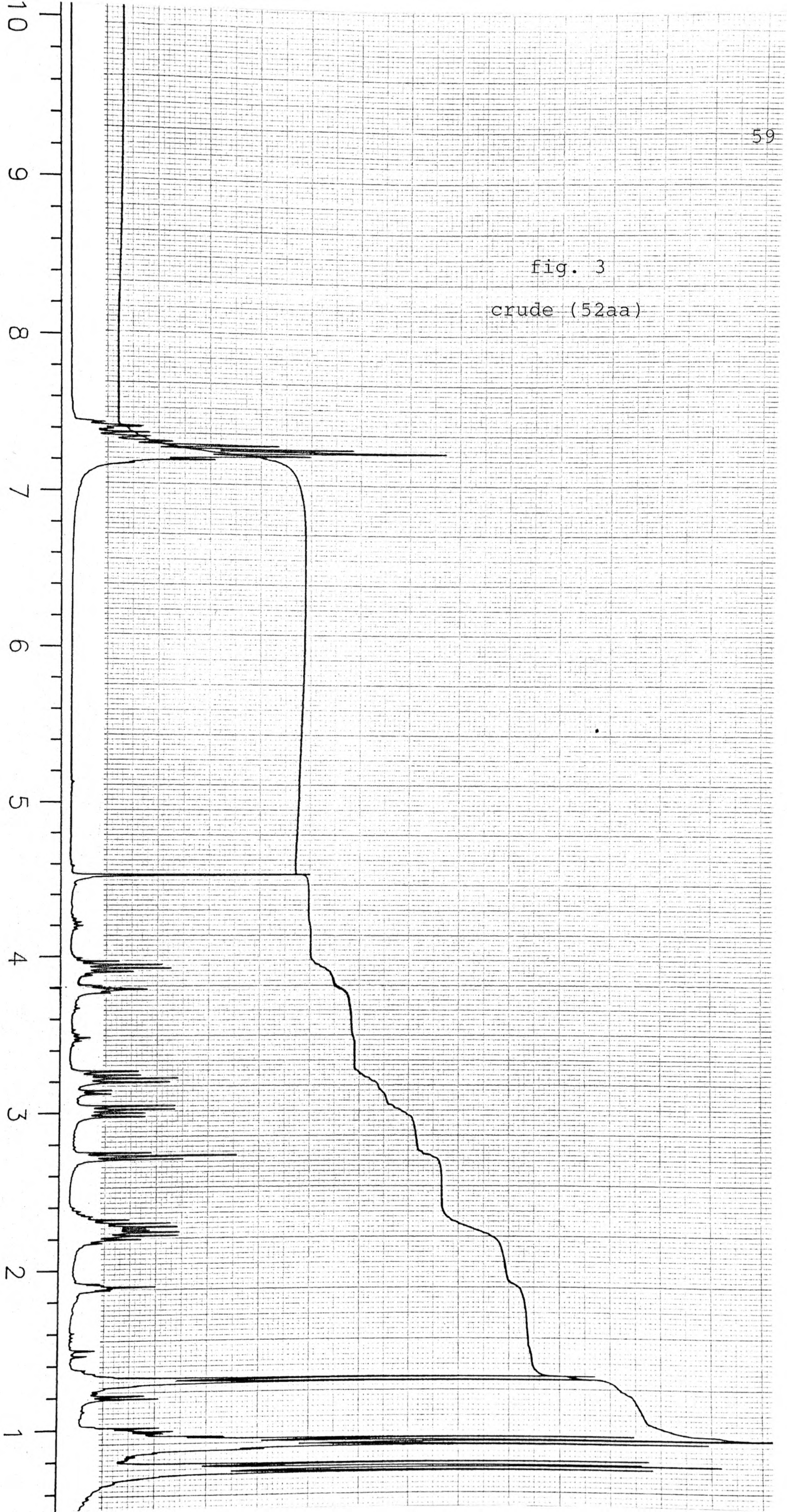


fig. 3

crude (52aa)

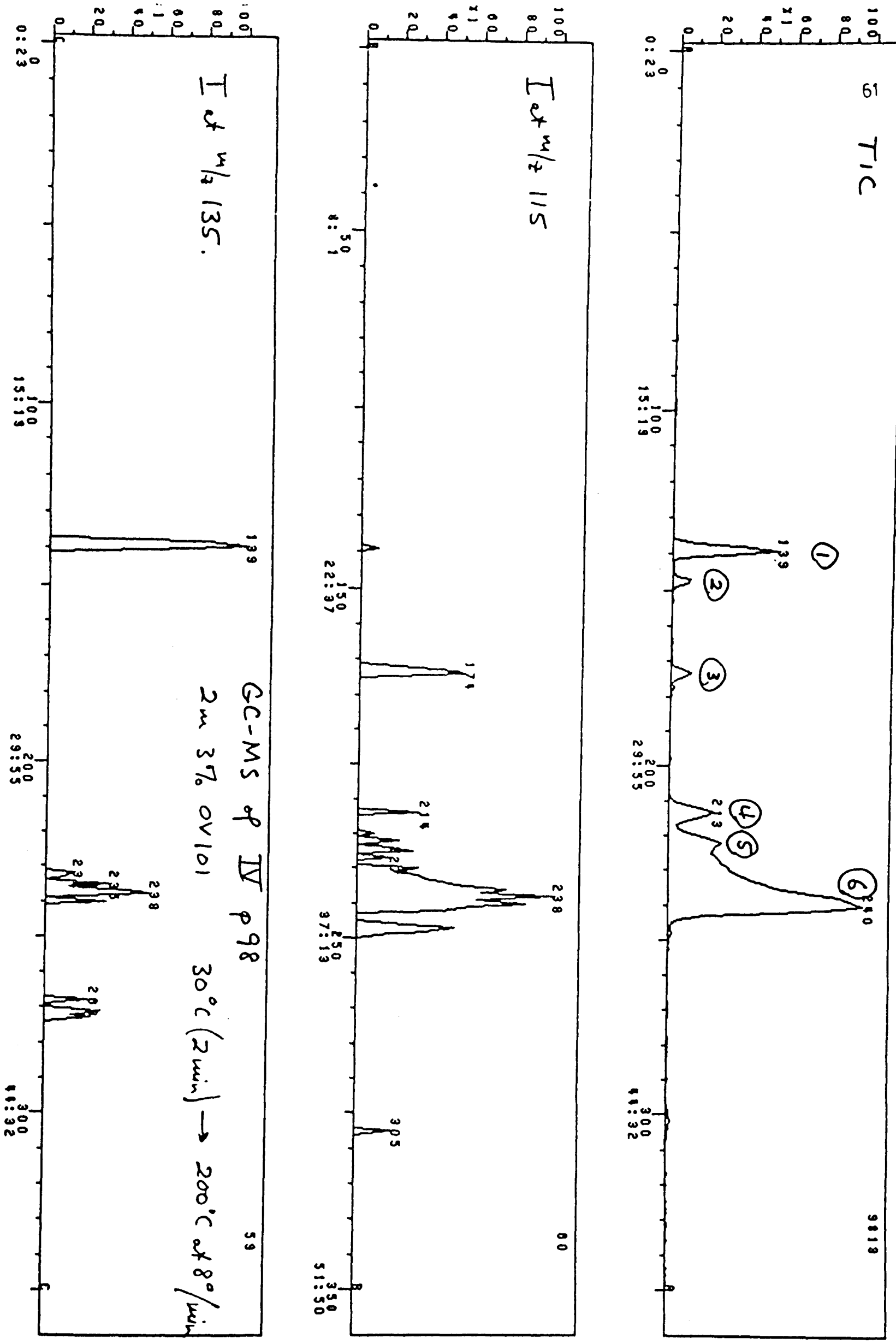
hydrazone			alkyl halide		azoalkane	
	R^1	R^2	R^5	X		yield/%
(51a)	Me	H	Bn	Br	(52aa)	66
(51k)	Et	H	Bn	Br	(52ka)	46
(51k)	Et	H	n-Bu	I	(52kb)	74

Table 13

The ease of reduction of the DMP azoalkanes (52) was investigated using 2-DMP azo-1-phenylpropane (52aa). Catalytic hydrogenation at low pressures gave unchanged starting material. When the reaction conditions were extended to 15h. in acetic acid with PtO_2 as catalyst and 50 atm. hydrogen pressure only unchanged azoalkane (52aa) was recovered.

The DMP hydrazone of phenylacetone (51l) was used as a model to study a feasible reduction system. Catalytic hydrogenation over 5% platinum on carbon in ethanol for 110h. at 25 atm. gave an extremely complex product which was analysed by g.c.m.s. (fig. 4). The major product (peak 6) was assigned as the hydrazine obtained by reduction of the C=N double bond to CH-NH. A smaller amount of a product whose m/e was consistent with the desired amine was present, (peak 1) there were also several other unassigned products.

Catalytic hydrogenation of DMP azo derivatives was not further investigated as no practicable method seemed likely to be developed. The DMP system is significantly more hindered than the systems that have been reported to be successfully cleaved.[110-114]



g.c.m.s. trace from hydrogenation of (511)

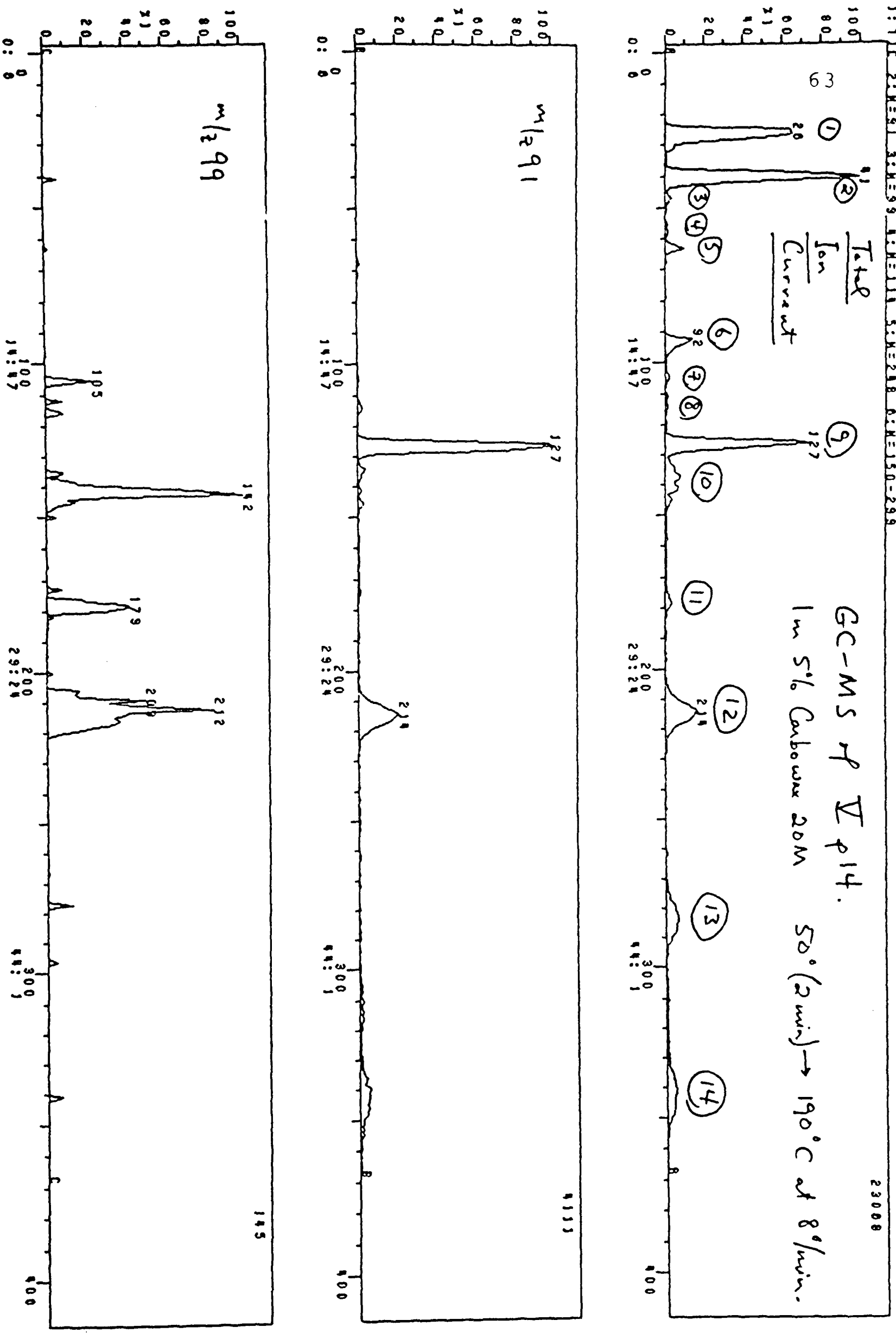
fig. 4

Other methods of reduction were also investigated. The azoalkane (52aa) was refluxed in acetic acid with excess zinc dust overnight. A complex product mixture was formed which was analysed by g.c.m.s.. (fig. 5) Included amongst the products were the starting azoalkane (52aa) (peak 12) and the N,N´dialkylhydrazine from reduction of the azoalkane. (peak 14)

Diborane has been used for the reduction of aromatic azo compounds[135] and tetraalkylhydrazines[136-138], though reduction of N,N´-dialkylhydrazines was reported not to proceed.[136] Azoalkane (52aa) was refluxed in THF for 24h. with 10 equivalents of diborane. Examination of the product by 300MHz n.m.r. spectroscopy showed that the azoalkane was unchanged. (Some butan-1-ol was produced by reduction of THF.[139])

The synthesis of ketones[55] and 4-ketoesters (chapter 2) from t-butylhydrazones involved tautomerisation with TFA of an azoalkane or a 4-azoester (LII) to the more stable t-butylhydrazone form (LIII). (scheme 30) Hydrolysis gave a ketone (LIV) and t-butylhydrazine (not isolated) (LV).

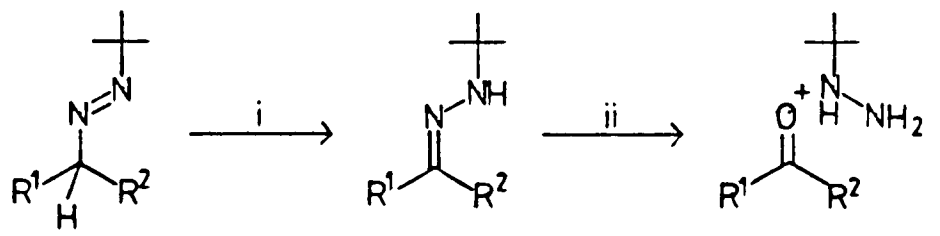
We reasoned that with a DMP azoalkane (52) tautomerisation could occur in the alternate sense to produce a hydrazone of 2,4-dimethylpentan-3-one. (scheme 31, path c, $R^3=R^4=$i-Pr) Hydrolysis of this hydrazone would produce 2,4-dimethylpentan-3-one and a new hydrazine synthesised by the synthetic equivalent of an α-hydrazino anion. The reduction of aliphatic hydrazines to amines has been reported,[140] consequently the isolation of a hydrazine



g.c.m.s trace from zinc-acetic acid reduction of (52aa)

fig. 5

would constitute a formal amine synthesis by an α-amino anion equivalent.



(LII) (LIII) (LIV)+(LV)

i TFA ii $(COOH)_2$ / H_2O / Et_2O

Scheme 30

The alkylation of ketone DMP hydrazones (51, R^1, R^2=alkyl) gave DMP azoalkanes (52) with R^1, R^2, R^5 all alkyl; consequently tautomerisation can only occur in one direction. The alkylation of aldehyde DMP hydrazones (51, R^1=alkyl, R^2=H) gave azoalkanes (52) with a secondary centre at each end of the azo linkage, thus tautomerisation could occcur in either or both of two directions.

Acetone DMP hydrazone (51b) was benzylated by the standard procedure. The crude 300MHz n.m.r. spectrum (fig. 6) showed clean C-benzylation. Treatment of the crude azoalkane (52ba) with TFA for 5h. gave the tautomerised hydrazone (55ba) cleanly (fig. 7). Aqueous oxalic acid failed to hydrolyse this hydrazone (55ba). This was not an unexpected result as we have observed the failure of this method to hydrolyse the t-butylhydrazones of the 4-keto-esters (3c) and (3g) (chapter 2). Reflux for 20h. with 1:1 THF:hydrochloric acid (2M) hydrolysed the hydrazone (55ba) but the hydrazine could not be isolated. Hydrolysis was successfully achieved with ethanol : hydrochloric acid

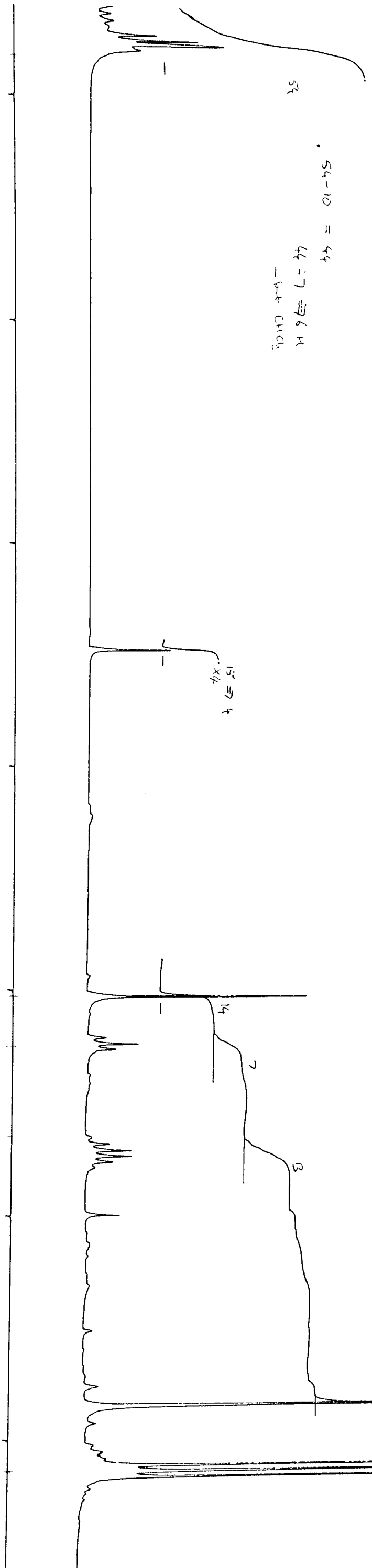


fig. 6

crude (52ba)

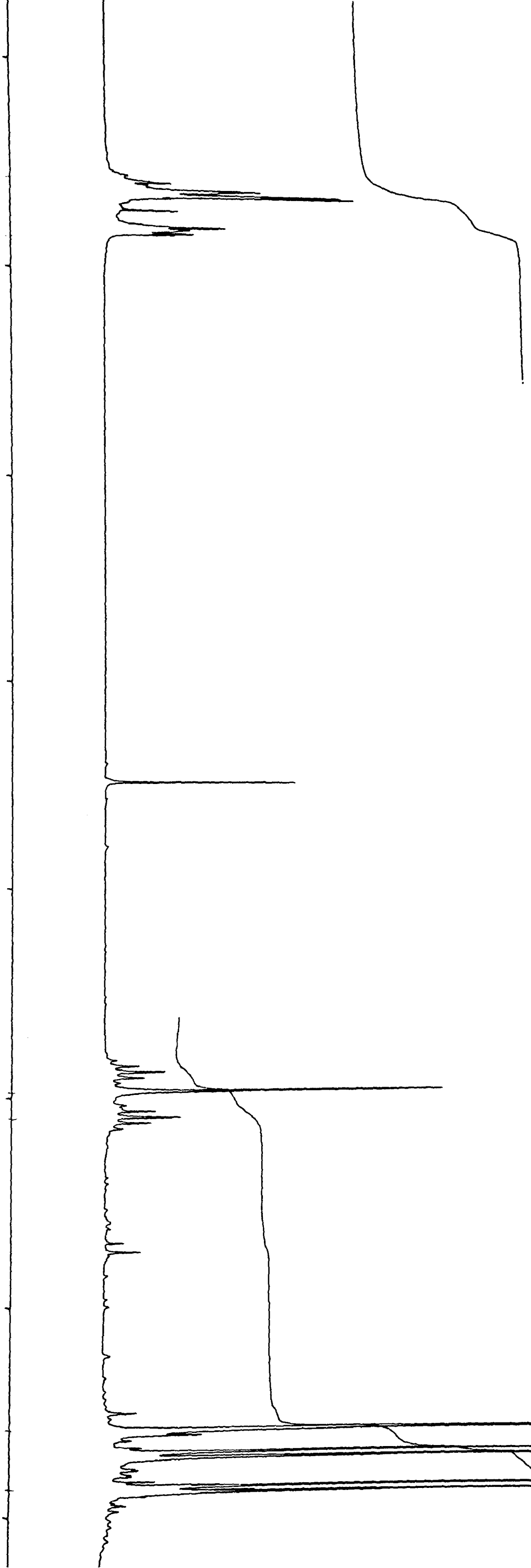


fig. 7

crude (55ba)

(concentrated)[141] for 16h. at room temperature, when the hydrazine hydrochloride (56ba) was isolated in 17% yield from starting hydrazone (51b). The poor yielding step of this synthesis was almost certainly the hydrolysis, Smith _et al_[141] reported a 60% yield of _t_-butylhydrazine from hydrolysis of benzophenone _t_-butylhydrazone by this method, but the present hydrazine could well be less stable toward acid catalysed decomposition. Lower yields than those reported by Smith _et al_ have been reported for other hydrolyses by this procedure.[106]

2-DMP azo-1-phenylpropane (52aa) was treated with TFA. Examination of the 300MHz n.m.r. spectrum (fig. 8, _cf_ fig. 3, fig. 7) was conclusive that that the product was phenylacetone DMP hydrazone (51l) by comparison with previously prepared material. (scheme 31, path e, $R^3=R^4=$_i_-Pr)

The investigations of the reactions of DMP hydrazones (51) have shown that a secondary alkyl group can be sufficiently sterically hindering to direct reaction of hydrazone anions to carbon. The DMP group appears to hinder hydrogenation almost as much as the _t_-butyl group and thus the DMP hydrazones are not practical α-amino anion equivalents. The alkylation, tautomerisation and hydrolysis of acetone DMP hydrazone (51b) provides a novel, if low-yielding synthesis of hydrazines by an α-hydrazino anion equivalent.

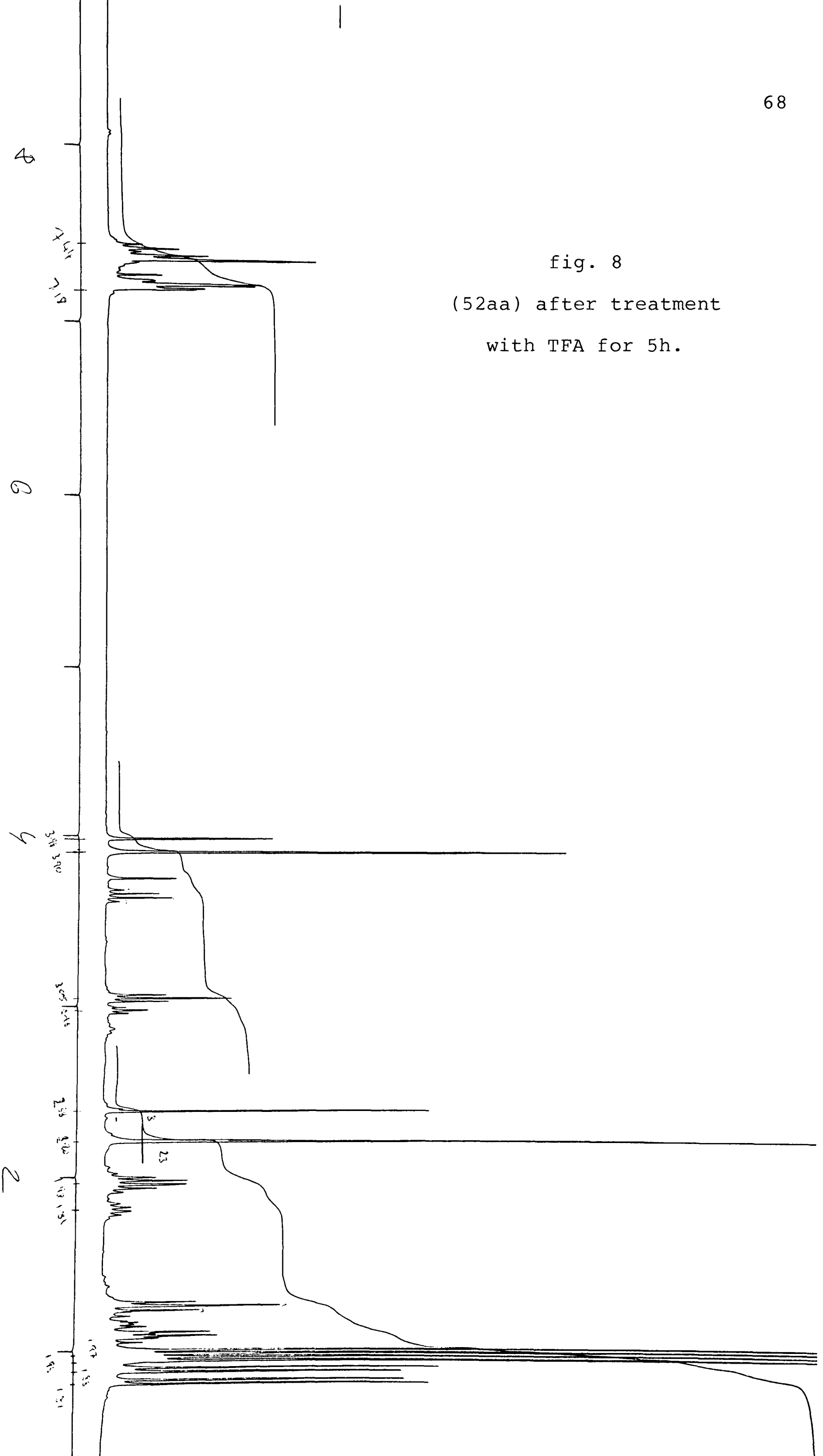
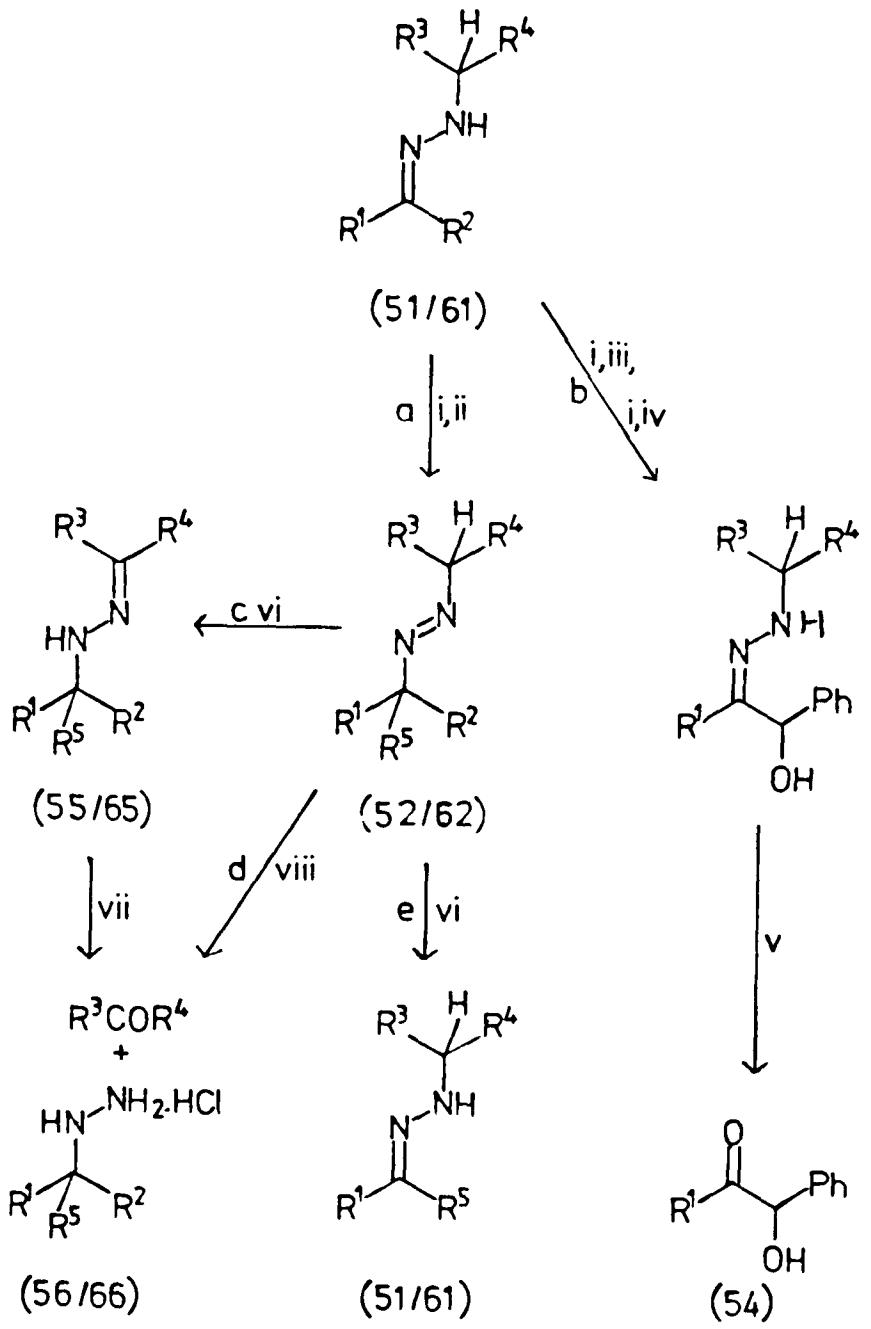


fig. 8

(52aa) after treatment

with TFA for 5h.



i n-BuLi ii R^5X iii PhCHO iv H_2O

v H_2O / Et_2O / $(COOH)_2$ vi TFA vii H^+ / H_2O

viii HCl / H_2O / Et_2O

Scheme 31

D. 3,3-Dimethylbut-2-ylhydrazones

As an alternative secondary alkylhydrazone system, with different steric requirements from DMP hydrazones we decided

to prepare 3,3-dimethylbut-2-ylhydrazones (t-butylmethyl hydrazones, TBM hydrazones) (61).

Pinacolone readily formed a BOC hydrazone with t-butyl-carbazate at room temperature. Attempted catalytic hydrogenation over 5% platinum on carbon catalyst was unsuccessful and only unchanged starting material was recovered. This was not a very surprising result as the C=N bond has an ∝-t-butyl group and, as in the reduction of t-butylazoalkanes, this is known to greatly hinder catalytic reduction. Alternative methods of reduction were tried, zinc in methanolic hydrogen chloride, aluminium amalgam in ethanol-ether,[142] sodium borohydride in methanol, lithium aluminium hydride in ether and sodium in ethanol (Bouveault-Blanc), all of which failed to reduce the C=N bond, only starting material was recovered in every case. The CBZ hydrazone of pinacolone was prepared using benzyl carbazate in an analogous manner to the BOC hydrazone. Reaction of the CBZ hydrazone with sodium in liquid ammonia gave the desired hydrazine (identified by 60MHz n.m.r.) but the isolated yield was never more than 5% and thus did not represent a practical synthesis. The problem was almost certainly in the isolation of the hydrazine rather than the reduction.

A low-yielding (13%) synthesis of the desired hydrazine has been reported.[143] The method used involved sodium borohydride reduction of pinacolone hydrazone, followed by acidification and work up. We argued that the reduction of the hydrazone could be occuring after acidification, when

the hydrazinium salt will be much more electrophilic than the free hydrazone, in competition with destruction of the borohydride. We reasoned that use of sodium cyanoborohydride under acidic conditions[144] might give a better yield of the hydrazine.

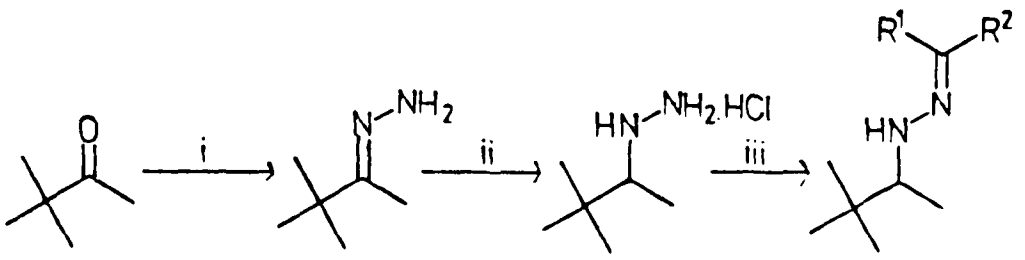
Pinacolone hydrazone (60) was prepared by the procedure of Mc Lean and Middleton[143] in 58% yield (the reported yield (89%) could not be reproduced). The hydrazone was dissolved in THF and sodium cyanoborohydride (0.7 mol equivalents, 2.1 H^- equivalents) was added, plus a crystal of methyl orange as an indicator. Hydrogen chloride in methanol was added to maintain the reaction at pH 3 (red-yellow transition of methyl orange). The reaction was stirred for 90 min. after the hydrogen chloride had been added. The solvents were removed to give the crude hydrazine hydrochloride (LVI), identified by the 60MHz n.m.r. (CD_3OD). TBM hydrazones (61) were prepared in variable yields using the method developed for acetaldehyde cyclohexylhydrazone (41a). (scheme 32) (table 14)

hydrazone	R^1	R^2	yield/%*
(61a)	Me	H	32
(61b)	Me	Me	62

* from (60)

Table 14

The presence of any remaining cyanoborohydride during the hydrazone formation did not cause any problem as the triethylamine ensured a basic solution for the reaction.



(60) (61)

i NH_2NH_2 / t-BuOH ii $NaCNBH_3$ / MeOH / HCl / THF

iii MeOH / CH_2Cl_2 / Et_3N / R^1COR^2

Scheme 32

Alkylation of the hydrazones was carried out using the standard procedure. Examination of the crude 300MHz n.m.r. spectra of the alkylation products showed no evidence for N-alkylation, but C-alkylated products (62) could be observed clearly. (fig. 9) (scheme 31, path a, R^3=t-Bu, R^4=Me) The azoalkanes were isolated in good yields. (table 15)

hydrazone			alkyl halide		azoalkane	
	R^1	R^2	R^5	X		yield/%
(61a)	Me	H	Bn	Br	(62aa)	47
(61b)	Me	Me	Bn	Br	(62ba)	73
(61b)	Me	Me	n-C_7H_{15}	I	(62bc)	68

Table 15

Examination of the 300MHz n.m.r. spectrum of the azoalkane (62aa) (fig. 9), which has two chiral centres (both racemic) reveals a diastereoisomer ratio of approximately 3:2. This implies that had enantiomerically pure hydrazine been used a 20% enantiomeric excess would have been obtained in the alkylated product. This is not of any practical use, but it demonstrates that selectivity can be

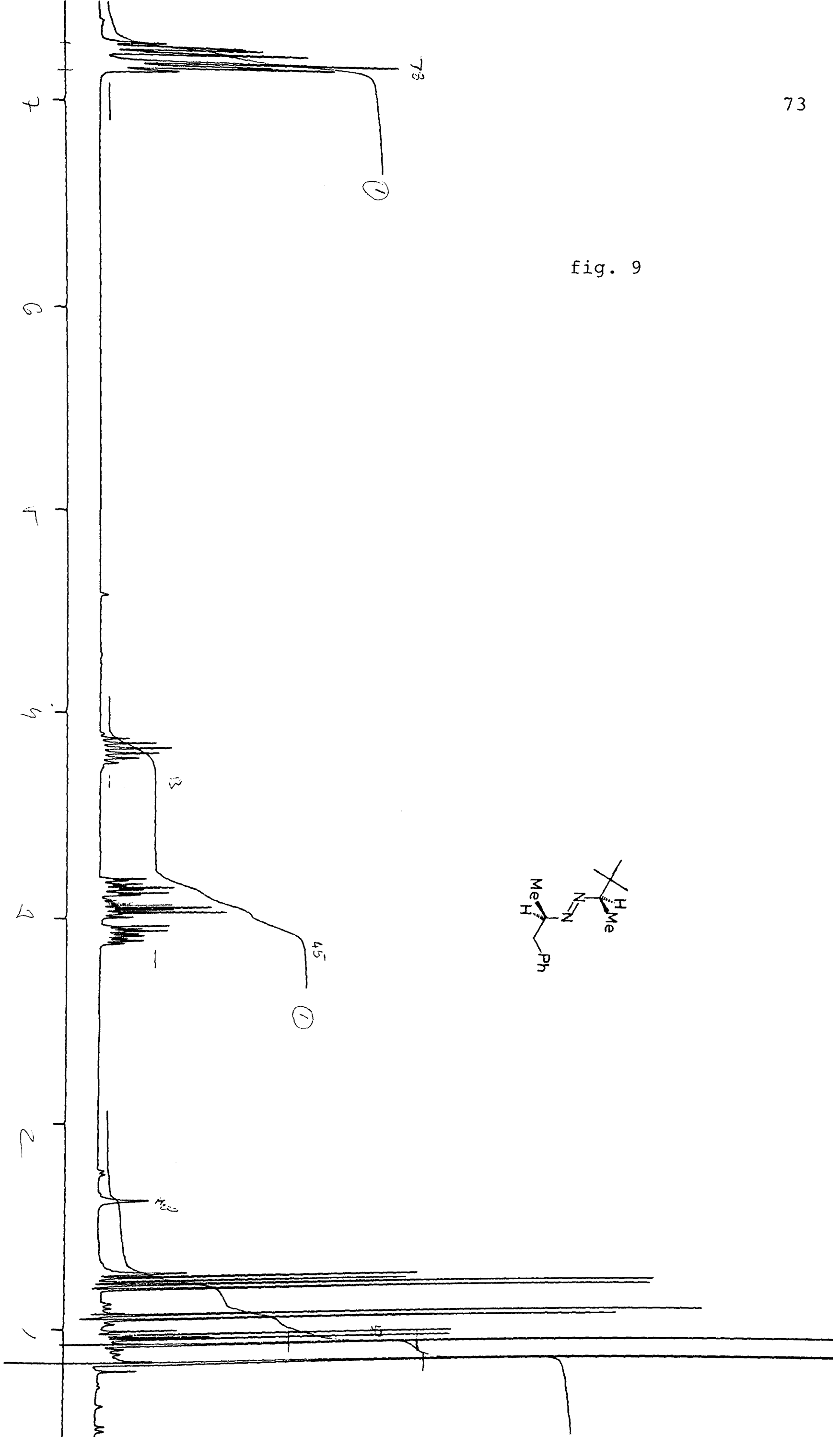


fig. 9

achieved, and it is possible that a more complex (probably chelating) hydrazone could give a useful induction.

Reaction of the anion of acetaldehyde TBM hydrazone with benzaldehyde followed by deprotonation, quenching and hydrolysis gave 1-hydroxy-1-phenylpropan-2-one (64a=54a) in 26% yield. (scheme 31, path b, R^3=t-Bu, R^4=Me)

The azoalkane (62ba) was tautomerised to the hydrazone form (65ba) by TFA (fig. 10). (scheme 31, path c, R^3=t-Bu, R^4=Me) The hydrazone (65ba) could be hydrolysed by oxalic acid-water-ether, but it proved difficult to isolate the hydrazine (56ba). An experimentally simpler procedure involved treating the azoalkane (62ba) with a 2-phase system of hydrochloric acid (2M)-ether for 16h. (scheme 31, path d, R^3=t-Bu, R^4=Me) Examination of the ether layer by 60 MHz n.m.r. showed the presence of pinacolone. The aqueous layer gave 2-methyl-1-phenylprop-2-ylhydrazine hydrochloride (66ba=56ba) in 38% yield from the azoalkane (62ba) (27% yield from the hydrazone (61b)). A similar tautomerisation and hydrolysis on azoalkane (62bc) gave the hydrazine hydrochloride (63bc) in 11% yield (7% from starting hydrazone (61b))

Treatment of the azoalkane (62aa) with TFA resulted in tautomerisation to a mixture of both possible hydrazones (61l) and (65aa) in a ratio of approximately 2:3 (fig. 11).

Direct catalytic hydrogenation of the azoalkanes (62) did not lead to the isolation of any amines. Hydrogenation of azoalkane (62bc) over palladium on carbon in ethanol

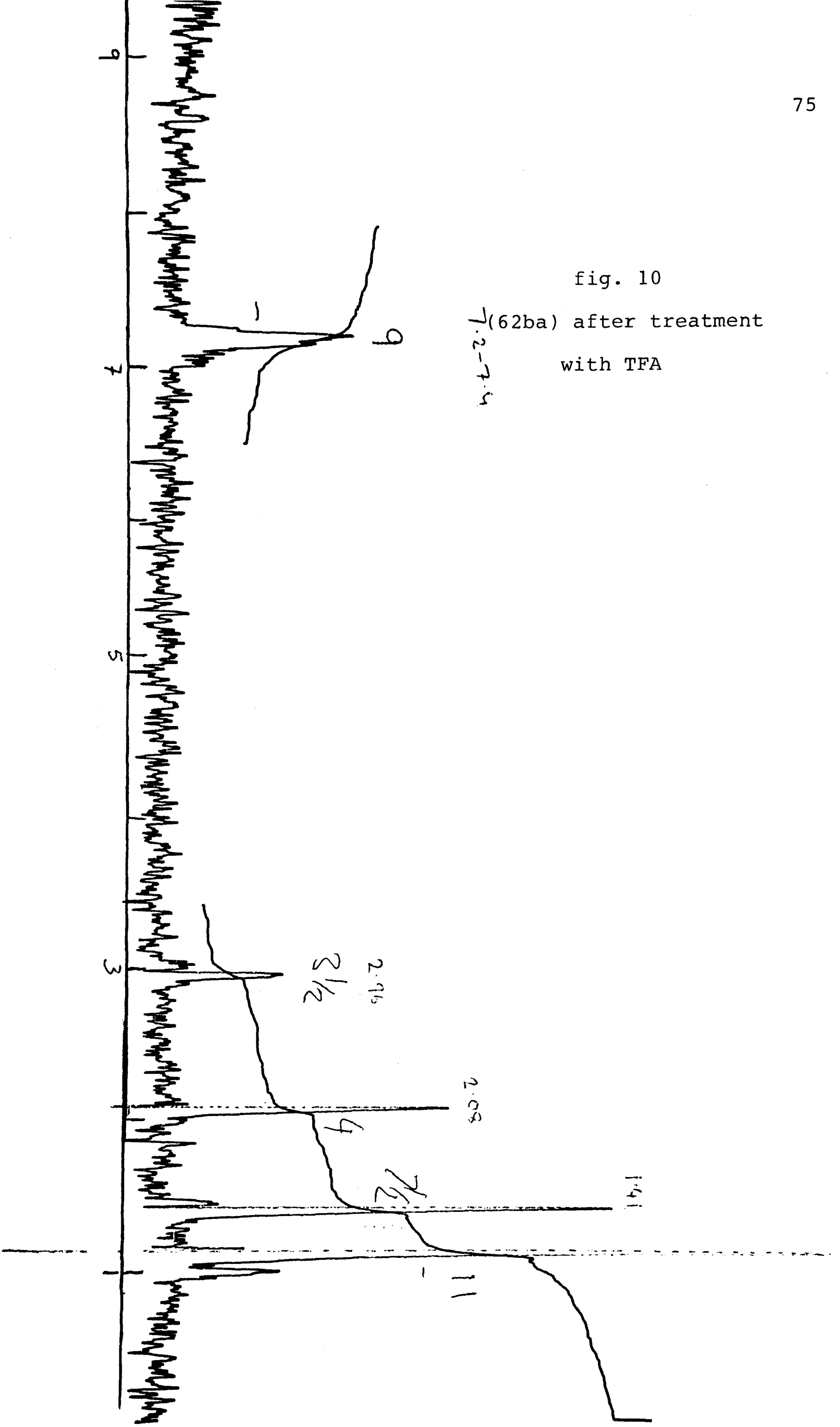


fig. 10

(62ba) after treatment with TFA

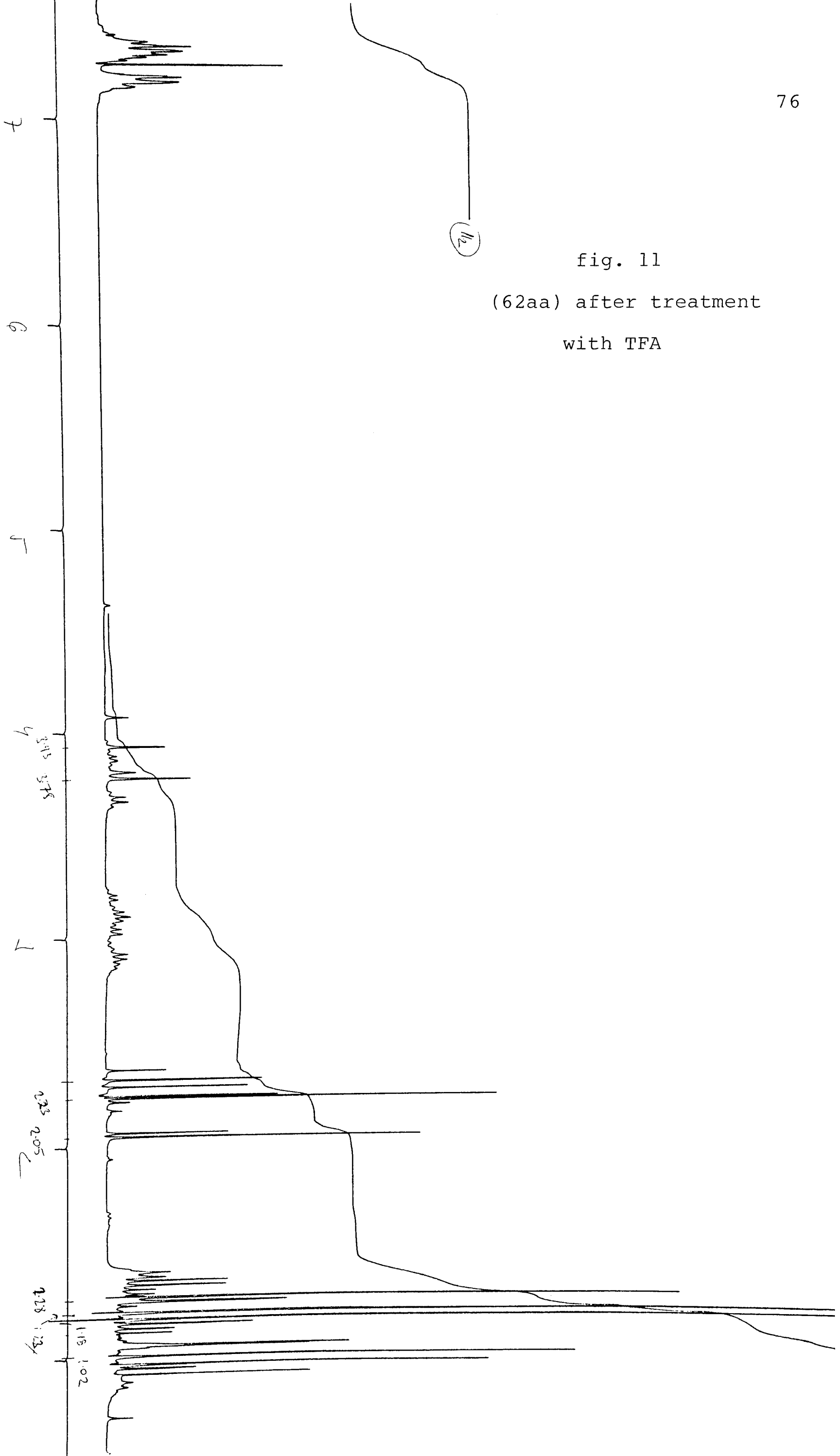


fig. 11

(62aa) after treatment

with TFA

containing concentrated hydrochloric acid was attempted. Crystallisation of the product gave the hydrazine hydrochloride (66bc) (8%) produced by tautomerisation and hydrolysis rather than the amine derived *via* reduction.

The hydrazine hydrochloride (66ba) was reduced by hydrazine and Raney-nickel in ethanol[140] to the amine (67ba) in 53% yield (equivalent to 14% from the hydrazone (61b)).

The synthesis of amines using a secondary alkyl hydrazone anion as an α-amino anion equivalent has thus been achieved for TBM hydrazones of ketones (61, R^1, R^2 =alkyl), albeit in a yield that is too low to be of synthetic significance. The reduction of the hydrazine (66ba=56ba) also formally demonstrates the use of DMP hydrazones (51) as α-amino anion equivalents as hydrazine (56ba) has also been prepared from acetone DMP hydrazone (51b).

The investigations of TBM hydrazones (61) have shown that their anions are sufficiently hindered to give reactions predominantly *via* carbon. The conversion of the derived azo alkanes (62) to hydrazones of pinacolone (65), followed by hydrolysis under mild conditions, gave the hydrazines (66) in better yields than the corresponding reactions of DMP hydrazones (51).

The synthesis of TBM hydrazine hydrochloride from pinacolone hydrazone by cyanoborohydride reduction provides a novel synthesis of secondary alkyl hydrazines. The yields of the TBM hydrazones (61) (32-62%) indicate that the

reduction gives a reasonable yield of the TBM hydrazine. If, as seems probable, this method is general, it would appear to be of considerable utility for the synthesis of hydrazines, particularly where catalytic hydrogenation can not be used.

Conclusions

The investigations of the anions of secondary alkyl hydrazones have shown that the balance between reaction at carbon and at nitrogen is quite finely dependent upon the steric bulk of the substituent on nitrogen. Thus simple secondary alkyl systems, isopropyl and cyclohexyl, result in small amounts of C-alkylation with alkyl halides. Systems of only moderately greater hindrance, 2,4-dimethylpent-3-yl with both α-positions tertiary, and 3,3-dimethylbut-2-yl with one α-quaternary centre and the other α-position primary, both gave essentially clean C-alkylation. Thus the first target, of developing secondary alkyl substituents that direct reaction to carbon was achieved successfully.

Investigation of the reductive cleavage of the azoalkanes produced by C-alkylation has been disappointing. The hindrance required to divert reaction to carbon appears also to retard catalytic hydrogenation to a negligible rate, which is, even in sterically unhindered molecules, a slow process. Other methods for reductive cleavage were investigated, but without success.

The prospects for developing a secondary system that directs reaction of the hydrazone anion to carbon, and at the same time allows catalytic hydrogenation of the resultant azoalkane seem poor. As a successful route to amines from hydrazone anions has been discovered using t-butyldiphenylmethylhydrazones[106] further investigations of secondary alkyl systems have not been pursued.

CHAPTER 5

Experimental

General Procedures

Reactions involving water or air sensitive reagents were carried out under an atmosphere of dry nitrogen unless otherwise stated. Nitrogen was dried through a closely packed column of calcium chloride and anhydrous silica gel.

Starting materials and reagents were purified and dried before use. Common solvents, dichloromethane, ether, ethyl acetate and petroleum were distilled prior to use for chromatography.

THF for organometallic reactions was dried by refluxing with potassium and benzophenone and distilling the blue solution onto fresh sodium wire. Ether for Grignard reactions was dried by standing with sodium wire for 24h..

Alkyl lithium reagents (n-butyl lithium in hexane, Aldrich; methyl lithium in ether, Aldrich) were titrated against 1,3-diphenylacetone tosylhydrazone,[146] They were added slowly to vigorously stirred reactions.

Reagents were purified by literature procedures[147] unless otherwise stated. Aldehydes were distilled from anhydrous calcium chloride and stored over 4Å molecular sieves, ketones were distilled from phosphorus pentoxide. Alkyl halides were dried with calcium chloride, distilled and stored over 4Å molecular sieves in the dark.

Temperatures were recoded in degrees Celsius. Low

temperatures were recorded as equilibrium bath temperatures.

Catalytic hydrogenations at increased pressures were carried out by the Hydrogenation Service, Pfizer Central Reaseach, with a Parr Hydrogenator, or with a Cook "Heated Type Low Pressure Catalyst Hydrogenation Apparatus".

Reaction mixtures were concentrated, usually at 25^{o} or below on a Buchi Rotavapor R; involatile compounds were further evaporated (<2mmHg).

T.l.c. was carried out on Merck 5554 aluminium backed $silica_{F254}$ plates. Developing solvents are given in parentheses. Visualisation was by ultraviolet light and acid charring (dodeca-molybdophosphoric acid in ethanol, 5% w/v), or, for carbonyl compounds, with Brady's reagent (dinitrophenylhydrazine: sulphuric acid: methanol; 1:1:18).

Column chromatography was carried out using Merck flash silica, 40-63 μm.

P.l.c. was carried out on Merck Kieselgel 60_{F254} 20x 20x 0.1 cm plates, prepared by Mr. R. F. Prior of The Dyson Perrins Laboratory.

Gas liquid chromatography (g.c.) was run on a Pye series 104 chromatograph with a 5'x 0.25" I.D. 3% OV1 on gas chrom Q (100-120 mesh) column.

Melting points (m.p.) were determined on a Buchi 510 capill.ary melting point apparatus and are uncorrected.

Infra-red (ν_{max}) spectra were recorded on a Perkin-Elmer 681 instrument (reference: polystyrene 1602 cm^{-1}) Broad (br), medium (m), strong (s) and significant weak (w) bands

were reported. Bands are quoted to ± 5 cm^{-1} (4000-2000 cm^{-1}) or ± 2 cm^{-1} (2000-600 cm^{-1}).

Ultraviolet (λ_{max}) spectra were recorded in acetonitrile solution on a Perkin-Elmer 555 spectrometer.

^{1}H N.m.r. spectra (δH) were recorded on Bruker WH 300, Bruker AM 250, Perkin-Elmer R24B or Nicolet QE 300 spectrometers operating at frequencies of 300MHz, 250MHz, 60MHz and 300MHz respectively. Spectra were recorded for samples in deuteriochloroform unless otherwise stated. Residual protiated solvent was used as reference ($C\underline{H}Cl_3$ =7.27ppm, $C\underline{H}D_2OD$ =3.305ppm), chemical shifts are expressed in parts per million on the δ scale relative to tetramethylsilane. Coupling constants were calculated from the print-out where available and are quoted to ± 1Hz. Each chemical shift is followed by parentheses containing the integral, the spin multiplicity, the coupling constant $\underline{J}$ (if applicable) and assignment of the signal. Multiplicities were recorded as br broad peak, s singlet, d doublet, t triplet, q quartet and m multiplet.

^{13}C N.m.r. spectra (δC) were recorded on Bruker AM 250, Nicolet QE 300 or Varian XL 100 spectrometers operating at 63.0MHz, 75.6MHz and 25.2MHz respectively. Spectra were recorded in deuteriochloroform solution unless otherwise stated. Both broad band decoupled (BB) and continuous wave (CW) spectra were recorded unless otherwise stated. The solvent was used as the reference ($\underline{C}DCl_3$ =77.00ppm, $\underline{C}D_3OD$ =49.00ppm), chemical shifts are expressed in parts per

million on the δ scale relative to tetramethylsilane. Each chemical shift is followed by parentheses containing the CW multiplicity (if available) and the assignment of the signal. For some spectra not all resonances were resolved.

Mass spectra (m/e) were recorded by the Mass Spectrometry Service, Dyson Perrins Labortory, on V. G. Analytical 16F, 30F or ZAB 1F spectrometers, or by the Analytical Control Department, Pfizer Central Research on a V. G. Analytrical 7070F spectrometer. High resolution mass spectra were recorded on the ZAB 1F in Oxford or on a V. G. Analytical 70E spectrometer in Sandwich. The mode is indicated as follows: E.I.: electron impact; NH_3 C.I.: ammonia chemical ionisation; NH_3 D.C.I. ammonia direct chemical ionisation; or I.B.E.I.: in beam electron impact.

Microanalyses were carried out by Dr. F. B. Strauss of the Dyson Perrins Labortory, the Analytical Control Department, Pfizer central research or the microanalysis service of Manchester University. Solids were recrystallised, liquids distilled and oils purified by p.l.c. prior to microanalysis.

Temperatures were reported in degrees Celsius.

Standard Hydrolysis Methods

Method A:

Crude product in ether (1ml/mmol) was stirred with oxalic acid (0.2g/mmol) in water (4ml/mmol) under an inert atmosphere for 3-16h.. The work up was by one the standard methods (vide infra)

Method B:

Crude product in THF:hydrochloric acid (2M) 1:1 (4ml/mmol) was heated under reflux for 16h. under an inert atmosphere. The solution was allowed to cool to room temperature, then concentrated to remove most of the THF. The product was worked up by one of the standard methods.

Standard Work Up Methods

Method C:

Ether (20ml) was added to the crude hydrolysis product which was then separated. The aqueous layer was then extracted with ether (2x 15ml). The ether layers were combined, washed with sodium bicarbonate solution (saturated, 30ml) and brine (30ml), dried (sodium sulphate), filtered and concentrated.

Method D:

As method C but omitting the bicarbonate wash.

Method E:

Ethyl acetate (20ml) was added to the crude hydrolysis product. Salt was added to saturate the aqueous layer. The layers were separated and the aqueous layer extracted with ethyl acetate (2x 15ml). The organic layers were combined, washed with sodium bicarbonate solution (saturated, 25ml) and brine (25ml), dried (sodium sulphate), filtered and concentrated.

Method F:

As method E, omitting the bicarbonate wash.

Experiments Described in Chapter 2

General Procedure for the Preparation of t-Butylhydrazones (1)

To t-butylhydrazine hydrochloride (62.3g, 0.50mol) and sodium hydroxide (20.0g, 0.50mol) in water (200ml) was added acetic acid (5ml, 0.09mol) and carbonyl compound (0.55mol). The solution was stirred for 2 h. under argon. The layers were separated and the aqueous layer extracted with ether (2x 50ml). The organic layers were combined, washed with brine (50ml), dried (sodium sulphate), filtered and concentrated. The product was distilled under vacuum from sodium hydroxide and calcium hydride.

Preparation of Acetone t-butylhydrazone (1b)

The general method was followed giving Acetone t-butylhydrazone[141] (1b) (40.9g, 72%), b.p. 40-41°/15mmHg (lit:[141] 132-134°); ν_{max} ($CHCl_3$) 3230w (N-H), 2930s, 2870s, 2835m, 1465m, 1420s, 1369s, 1342s, 1262m, 1092m, 1046m, 988m and 646m cm^{-1}; δH (R24) 1.14 (9H, s, t-Bu), 1.66, 1.87 (6H, 2x s, 2x CH_3) and 4.00 (1H, br, NH); m/e (NH_3 C.I.) 129 (MH^+, 100%), 128 (M^+, 16), 113 (99), 72 (25) and 56 (40); m/e (E.I.) 128 (M^+, 20%), 113 (100), 72 (30), 57 (56), 56 (74) and 55 (32); analysis found: C:65.4, H:12.6, N:22.0%; $C_7H_{16}N_2$ requires C:65.6, H:12.6, N:21.9%.

Similarly prepared:

Acetaldehyde t-butylhydrazone (1a) as a mixture of

isomers (E:Z ~60:40) (38.8g, 68%); b.p.86-91/195mmHg; ν_{max} (film) 3380w, 3240w, 2975s, 2915s, 2870s, 1476m, 1457m, 1386m, 1361s, 1258m, 1230s, 1216m, 1137m, 1093m, 1025m and 873m cm^{-1}; δH (WH 300) 1.16, 1.21 (9H, 2x s, $C(C\underline{H}_3)_3$), 1.71, 1.86 (3H, 2x d, J 5Hz, 2-$C\underline{H}_3$), 4.31 (1H, br, N$\underline{H}$), 6.65 and 7.04 (1H, 2x q, J 5Hz, $\underline{H}C{=}N$); δC (AM 250) 11.51, 17.66 (2x q, 2-$\underline{C}H_3$), 28.12, 28.33 (2x q, $C(\underline{C}H_3)_3$) 52.56, 52.64 (2x s, $\underline{C}Me_3$), 135.35 and 137.46 (2x d, H$\underline{C}$=N); m/e (NH_3 C.I.) 115 (MH^+, 100%) and 99 (10); m/e (E.I.) 114 (M^+, 29%) and 99 (100); M^+ (E.I.) found: 114.1157; $C_6H_{14}N_2$ requires: 114.1157.

Isobutyraldehyde t-butylhydrazone (1c) as a mixture of isomers (E:Z ~93:7) (59.3g,73%) ; b.p. 59.5-61.5°/18mmHg; ν_{max} (film) 3230w (N-H), 2965s, 2935s, 2870m, 1469m, 1457m, 1447m, 1386m, 1363m, 1234m, 1216m, 1105m, 1086m, 1070m and 1027m cm^{-1}; δH (WH 300) 1.04, 1.06 (6H, 2x d, J 7Hz, $CH(C\underline{H}_3)_2$), 1.16, 1.19 (9H, 2x s, $C(C\underline{H}_3)_3$), 2.40-2.50,2.57-2.71 (1H, 2x m, $C\underline{H}Me_2$), 3.72 (1H, br, N$\underline{H}$), 6.33 and 6.94 (1H, 2x d, J 5Hz, $\underline{H}C{=}N$); δC (AM 250) 19.25, 20.07, 28.09, 28.21 (4x q, 2x $CH(\underline{C}H_3)_3$), 30.97 (d, $\underline{C}HMe_2$), 52.91 (s, $\underline{C}Me_3$), 147.05 and 147.53 (2x d, H$\underline{C}$=N); m/e (E.I.) 142 (M^+, 19%), 127 (100), 71 (24), 58 (43), 57 (41), 42 (23), 41 (14) and 39 (32); analysis found C:67.5,H:12.7,N:19.5%; $C_8H_{18}N_2$ requires C:67.6,H:12.8,N:19.7%.

Pentanal t-butylhydrazone (1d) as a mixture of isomers (E:Z ~3:1) (68.7g, 88%); b.p. 70-72°/14mmHg; ν_{max} (film) 3235w (N-H), 2960s, 2930s, 2875s, 2865s, 1467m, 1452m,

1387m, 1370m, 1234m, 1216 and 1097m cm^{-1}; δH (WH 300) 0.90, 0.93 (3H, 2x t, J 7Hz, 5-C$\underline{H}_3$), 1.16, 1.19 (9H, 2x s, C(C$\underline{H}_3$)$_3$), 1.19-1.55 (4H, m, 3,4-C$\underline{H}_2$), 2.04, 2.18 (2H, 2x t of d, J 7Hz, 5Hz, 2-C$\underline{H}_2$), 3.65 (1H, br, N$\underline{H}$), 6.48 and 7.01 (1H, 2x t, J 5Hz, 1-C$\underline{H}$); δC (AM 250) 13.12 (q, 5-$\underline{C}H_3$), 21.53, 21.85 (2x t, 4-$\underline{C}H_2$), 24.83, 26.86 (2x t,3-$\underline{C}H_2$), 27.69, 27.83 (2x s, C($\underline{C}H_3$)$_3$), 28.50, 31.25 (2x t, 2-$\underline{C}H_2$), 52.27, 52.36 (2x s, $\underline{C}Me_3$), 140.54 and 141.15 (2x s, 1-$\underline{C}$H); m/e (E.I.) 156 (M^+, 14%), 141 (100), 58 (51), 57 (27) and 41 (19); analysis found C:69.3, H:13.0, N:17.7%; $C_9H_{20}N_2$ requires C:69.2, H:12.9, N:17.9%.

Cyclohexanone t-butylhydrazone (1e) (53.0g, 54%); b.p.104-106°/15mmHg; ν_{max} (film) 3540-3160br w (N-H), 2930s, 2860s, 1631w, 1476m, 1449m, 1437m, 1387m, 1361s, 1238s, 1220s, 1138m, 1112m, 1079m, 1068m and 1024m cm^{-1}; δH (WH 300) 1.15 (9H, s, C(C$\underline{H}_3$)$_3$), 1.58 (6H, br, 3,4,5-C$\underline{H}_2$), 2.16, 2.19 (4H, 2x t, J 6Hz, 2,6-C$\underline{H}_2$) and 4.15 (1H, br, N$\underline{H}$); δC (AM 250) 24.45, 25.30, 25.66, 26.74, 35.23 (5x t, 2,3,4,5,6-$\underline{C}H_2$), 28.14 (q, C($\underline{C}H_3$)$_3$), 52.57 (s, $\underline{C}Me_3$) and 149.64 (s, $\underline{C}$=N); m/e (NH_3 C.I.) 169 (MH^+, 100%) and 153 (19); m/e (E.I.) 168 (M^+, 33%), 153 (100), 112 (11), 96 (43), 69 (20), 58 (22), 57 (23), 55 (37), 54 (15), 41 (25) and 40 (37); M^+ (E.I.) found: 168.1626; $C_{10}H_{20}N_2$ requires: 168.1626.

Octanal t-butylhydrazone (1f) as a mixture of isomers (E:Z ~3:1), (58.5g, 59%) b.p. 82-84°/1.2mmHg, ν_{max} (film) 3365w (N-H), 3233w (N-H), 2960s, 2930s, 2910s, 2870s, 1478m, 1464s, 1451m, 1387m, 1361s, 1253m, 1232s, 1217s,

1096m, 1025m and 919m cm^{-1}; δH (WH 300) 0.88, 0.89 (3H, 2xt, J 7Hz, $CH_2C\underline{H}_3$), 1.16, 1.19 (9H, 2x s, t-Bu), 1.27-1.33 (8H, br, $CH_2(C\underline{H}_2)_4Me$), 1.41-1.56 (2H, m, 3-$C\underline{H}_2$), 2.03, 2.17 (2H, 2x t of d, J 7Hz, 5Hz, 2-$C\underline{H}_2$), 4.91 (1H, br, N$\underline{H}$), 6.48 and 7.00 (1H, 2x t, J 5Hz, $C\underline{H}$=N); δC (AM 250) 13.87 (q, 8-$\underline{C}H_3$), 22.45, 25.70, 26.15, 26.90, 28.87, 28.96, 29.27, 31.57, 31.65, 32.08 (10x t, all $\underline{C}H_2$), 28.24, 28.36 (2x q, $C(\underline{C}H_3)_3$), 52.88, 52.94 (2x s, $\underline{C}Me_3$), 141.84 and 142.52 (2x s, H$\underline{C}$=N) ; m/e (NH_3 C.I.) 199 (MH^+, 62%), 198 (M^+, 11), 183 (100), 114 (10), 58 (61) and 57 (49); m/e (E.I.) 198 (M^+, 7%), 183 (58), 114 (5), 71 (10), 58 (45) and 57 (100); M^+ (E.I.) found 198.2050; $C_{12}H_{26}N_2$ requires 198.2050.

Benzaldehyde t-butylhydrazone (1g) (as a single isomer) (75.7g, 85%); b.p.91-93°/1.7mmHg; ν_{max} (film) 3250w (N-H), 3065m, 3030m, 2975s, 2930m, 2905m, 2875m, 1598m, 1569m, 1482m, 1474m, 1446m, 1389m, 1361m, 1231m, 1213m, 1119m, 1072m, 1027m, 928m, 758s and 695s cm^{-1}; δH (WH 300) 1.28 (9H, s, $C(C\underline{H}_3)_3$), 4.67 (1H, br, N$\underline{H}$), 7.22-7.48, 7.58-7.60 (5H, m, Ph) and 7.63 (1H, s, $\underline{H}$C=N); m/e (NH_3 C.I.) 177 (MH^+, 100%) and 161 (15); m/e (E.I.) 176 (M^+, 48%), 161 (100), 106 (18), 105 (44), 78 (12), 77 (31), 58 (10), 57 (20), 51 (15) and 41 (14); analysis found C:75.1, H:9.3, N:15.7; $C_{11}H_{16}N_2$ requires C:75.0, H:9.2, N:15.9.

General Procedure For Michael Additions Of Hydrazone Anions

To a solution of t-butylhydrazone (1),(5.0mmol) in THF (10ml) at 0° was added n-butyl lithium (4.75mmol) and the

reaction stirred for 10 min. The reaction was cooled to -78°. After 10 min. Michael acceptor (5.0mmol) was added and the reaction stirred for 30 min.

Crude azo compounds (2) were obtained by quenching with acetic acid (0.5ml), adding petroleum (25ml), warming to room temperature, filtering and concentrating.

Crude ketones (3,4) were obtained by adding TFA (2.5ml), warming to room temperature, stirring for 80-300 min.,removal of volatiles by concentration, and hydrolysis.

Preparation of (±)-Methyl 3-(1-t-butylazocyclohexyl)-butanoate (2e)

The general procedure for Michael additions was followed using cyclohexanone t-butylhydrazone (1e) and methyl crotonate. The crude azoester (2e) was purified by column chromatography (60g silica, eluant (i) ether:petroleum; 1:24 (200ml) (ii) ether:petroleum; 1:9 (300ml)) yield 0.946g. Further purification of a sample (303mg) by p.l.c. (3 plates eluant ether:petroleum; 1:19) gave the title azoester (2e) (205mg, 50%); t.l.c. (ether:petroleum; 1:4) R_f0.6; ν_{max} (film) 2980s, 2960s, 2940s, 2875m, 1745s (C=O), 1453m, 1438m, 1386m, 1363m, 1303m, 1276m, 1258m, 1198m, 1177m and 1021m cm^{-1}; δH (WH 300) 0.87 (3H, d, J 7Hz, $CHC\underline{H}_3$), 1.20 (9H, s, $C(C\underline{H}_3)_3$), 1.41-1.60, 1.96-2.06, (10H, 2x br, 5x $C\underline{H}_2$ of ring), 1.90-1.98 (1H, m, $CH\underline{H}COOMe$), 2.20-2.31 (1H, m, $C\underline{H}CH_3$), 2.53-2.59 (1H, m, $C\underline{H}HCOOMe$) and 3.66 (3H, s, $COOC\underline{H}_3$); δC 14.18 (q, 4-$\underline{C}H_3$), 26.98 (q, $C(\underline{C}H_3)_3$), 21.83, 21.92, 25.89, 30.69, 31.85 (5x t, $C(\underline{C}H_2)_5$), 35.91 (t, 2-$\underline{C}H_2$), 37.65 (d, 3-$\underline{C}$H), 51.39 (q,

OCH_3), 67.35,70.27 (2x s, C -N=N-C) and 174.36 (s, COOMe); m/e (NH_3 C.I.) 269 (MH^+, 58%), 183 (32), 151 (30), 123 (22), 109 (100), 81 (31), 67 (21), 57 (18) and 41 (33); m/e (E.I.) 183 (14%), 151 (24), 133 (13), 123 (17), 109 (100), 81 (26), 67 (32), 57 (16), 55 (14) and 41 (21); analysis found C:67.1, H:10.4, N:10.1%; $C_{15}H_{28}N_2O_2$ requires C:67.1, H:10.5, N:10.4%.

Similarly Prepared:

From acetone t-butylhydrazone (1b) and methyl crotonate:

(±)-Methyl 3,4-dimethyl-4-(t-butylazo)pentanoate (2b) (58%); t.l.c. (ether:petroleum; 1:3) R_f0.5; ν_{max} (film) 2975s, 2935m, 2875m, 1745s (C=O), 1457m, 1439m, 1378m, 1365s, 1297m, 1260m, 1199m, 1180m, 1155m, 1110m, 1047m, 1036m and 1016m cm^{-1}; δH (WH 300) 0.95 (3H, d, J 7Hz, $CHCH_3$), 1.01, 1.04 (6H, 2x s, $C(CH_3)_2$), 1.16 (9H, s, $C(CH_3)_3$), 2.01-2.09 (1H, m, CHHCOOMe), 2.43-2.49 (1H, m, CHMe), 2.51-2.57 (1H, m, CHHCOOMe) and 3.68 (3H, s, OCH_3); δC (AM 250) 14.89, 21.05, 22.63 (3x q, 3x CH_3), 26.75 (q, $C(CH_3)_3$), 36.74 (t, CH_2), 38.59 (d, CH), 51.42 (s, OCH_3), 66.56, 69.77 (2x s, C-N=N-C) and 174.12 (s, COOMe); m/e (NH_3 C.I.) 229 (MH^+, 94%), 143 (77), 111 (50), 83 (100), 69 (46), 57 (57), 55 (30) and 41 (52); m/e (E.I.) 143 (24%), 111 (33), 83 (100), 69 (71), 57 (95), 55 (51) and 41 (98); analysis found C:63.2, H:10.3, N:12.4%; $C_{12}H_{24}N_2O_2$ requires C:63.1, H:10.6, N:12.3%.

From isobutyraldehyde t-butylhydrazone (1c) and methyl crotonate:

(±)-Methyl 3,5-dimethyl-4-(t-butylazo)hexanoate (2c) (54%);

t.l.c. (dichloromethane) R_f0.2; ν_{max} (film) 2970s, 2935m, 2875m, 1742s (C=O), 1472m, 1458m, 1436m, 1387m, 1364m, 1271m, 1254m, 1195m, 1174m, 1139m and 1081m cm^{-1}; δH (WH 300) 0.82-0.90 (9H, m, 3x C$\underline{H}_3$), 1.22 (9H, s, C(C$\underline{H}_3$)$_3$), 2.03-2.12, 2.54-2.59 (2H, 2x m, C$\underline{H}_2$COOMe), 2.22-2.27 (1H, m, C$\underline{H}$Me$_2$), 2.59-2.60 (1H, m, 3-C$\underline{H}$CH$_3$), 2.77-2.81 (1H, m, 4-C$\underline{H}$) and 3.68 (3H, s, OC$\underline{H}_3$); δC (AM 250) 17.60, 18.31, 19.86 (3x q, CH(C$\underline{H}_3$)$_2$,3-CHC$\underline{H}_3$), 27.07 (q, C(C$\underline{H}_3$)$_3$), 28.22 (d, 5-C$\underline{H}$), 30.89 (d, 3-C$\underline{H}$), 36.86 (t, 2-C$\underline{H}_2$), 51.39 (q, OC$\underline{H}_3$), 67.62 (s, C$\underline{M}$e$_3$), 86.48 (d, 4-C$\underline{H}$) and 173.81 (s, C$\underline{O}$OMe); m/e (NH_3 C.I.) 243 (M^+, 100%); analysis found: C:64.6, H:10.5, N:11.7%; $C_{13}H_{26}N_2O_2$ requires: C:64.4, H:10.8, N:11.6%.

From benzaldehyde t-butylhydrazone (1g) and methyl crotonate:

Methyl 3-(R,S)-4-(R,S)-3-methyl-4-phenyl-4-(t-butylazo)-butanoate (2g) (68%); t.l.c. (ether:petroleum; 1:3) R_f0.4; ν_{max} (film) 3090w, 3065w, 3030w, 2975m, 2935m, 2880m, 1739s (C=O), 1476m, 1473m, 1454m, 1436m, 1382m, 1364m, 1311m, 1252m, 1237m, 1198m, 1170m, 1011m, 763m and 604m cm^{-1}; δH (WH 300) 0.88 (3H, d, J 7Hz, CHC$\underline{H}_3$), 1.20 (9H, s, C(C$\underline{H}_3$)$_3$), 2.04-2.12, 2.42-2.49 (2H, 2x m, 2-C$\underline{H}_2$), 2.81-2.89 (1H, m, 3-C$\underline{H}$), 3.66 (3H, s, OC$\underline{H}_3$), 4.17 (1H, d, J 9Hz, 4-C$\underline{H}$) and 7.28-7.40 (5H, m, Ph); δC (AM 250) 16.76 (q, 3-CHC$\underline{H}_3$), 26.80 (q, C(C$\underline{H}_3$)$_3$), 35.54, (d, 3-C$\underline{H}$), 37.58 (t, 2-C$\underline{H}_2$), 51.41 (q, OC$\underline{H}_3$), 67.51 (q, C$\underline{M}$e$_3$), 86.00 (d, 4-C$\underline{H}$), 127.22, 128.10, 128.29 (3x d, C$\underline{H}$ of Ph), 139.59 (s, $\underline{C}_{ipso}$) and 173.14 (s, C$\underline{O}$OMe); m/e (NH_3 C.I.) 277 (MH^+, 100%) and 210

(17); analysis found C:69.7, H:8.7, N:9.9%; $C_{16}H_{24}N_2O_2$ requires C:69.5, H:8.8, N:10.1%.

Preparation of (±)-Methyl 3-methyl-4-oxopentanoate (3a)

The general procedure for Michael additions was followed using acetaldehyde t-butylhydrazone (1a) and methyl crotonate. The crude hydrazone was hydrolysed (method A, work up D) and the ketoester purified by column chromatography (50g silica, eluant ether:dichloromethane; 1:39) yield 0.507g. Further purification of a sample (270mg) by p.l.c. (3 plates, eluant dichloromethane) gave the title ketoester[148] (3a) (210mg, 58%); t.l.c. (ether:dichloromethane; 1:39)R_f0.2; ν_{max} 2975m, 2960m, 2885m, 1739s (C=O,ester), 1717s (C=O,ketone), 1464m, 1442m, 1437m, 1413m, 1360m, 1276m, 1204s, 1167s, 1127m, 1086m, 1015m and 1011m cm^{-1}; δH (WH 300) 1.16 (3H, d, J 7Hz, $CHC\underline{H}_3$), 2.23 (3H, s, 5-$C\underline{H}_3$), 2.27-2.34, 2.73-2.82 (2H, 2x m,$C\underline{H}_2COOMe$), 2.99-3.06 (1H, m, 3-C$\underline{H}$) and 3.67 (3H, s, $OC\underline{H}_3$); δC (AM 250) 16.40 (q, $CH\underline{C}H_3$), 28.22 (q, 5-$\underline{C}H_3$), 36.19 (t, $\underline{C}H_2COOMe$), 42.62 (d, 3-$\underline{C}$H), 51.54 (q, $O\underline{C}H_3$), 172.58 (s, $\underline{C}OOMe$) and 210.48 (s, $\underline{C}$=O); m/e (NH_3 C.I.) 162 (MNH_4^+, 87%), 145 (MH^+, 22) and 35 (100); m/e (E.I.) 144 (M^+, 1%), 113 (15), 102 (12), 87 (18), 84 (12), 60 (24), 59 (19) and 43 (100); analysis found C:58.6, H:8.5%; $C_7H_{12}O_3$ requires C:58.3, H:8.4%.

Similarly Prepared:

From pentanal t-butylhydrazone (1d) and methyl crotonate:

(±)-Methyl 3-methyl-4-oxooctanoate (3d) (60%); t.l.c. (ether:dichloromethane; 1:19) R_f0.4; ν_{max} (film) 2960s, 2935m, 2875m, 1738s (C=O,ester), 1715s (C=O,ketone), 1462m, 1453m, 1435m, 1408m, 1378m, 1359m, 1270m, 1199s, 1176s, 1123m, 1103m, 1042m, 1007m and 710m cm^{-1}; δH (WH 300) 0.92 (3H, t, J 7Hz, 8-CH_3), 1.13 (3H, d, J 7Hz, $CHCH_3$), 1.32 (2H, ca sextet, J 8Hz, 7-CH_2), 1.59 (2H, ca quintet, J 7Hz, 6-CH_2), 2.26-2.33, 2.75-2.83 (2H, 2x m, CH_2COOMe), 2.50-2.56 (2H, m, 5-CH_2), 2.98-3.05 (1H, m, 3-CH) and 3.66 (3H, s, OCH_3); δC (AM 250) 13.75 (q, 8-CH_3), 16.65 (q, $CHCH_3$), 22.27 (t, 7-CH_2), 25.63 (t, 6-CH_2), 36.65 (t, 2-CH_2), 40.77 (t, 5-CH_2), 41.95 (d, 3-CH), 51.48 (q, OCH_3), 172.63 (s, COOMe) and 212.69 (s, C=O); m/e (NH_3 C.I.) 187 (MH^+, 100%), 172 (12) and 155 (29); m/e (E.I.) 155 (100%), 85 (36) and 57 (29); analysis found C:64.7, H:9.9%; $C_{10}H_{18}O_3$ requires C:64.5, H:9.7%.

From octanal t-butylhydrazone (1f) and methyl crotonate: (±)-Methyl-3-methyl-4-oxoundecanoate (3f) (50%); t.l.c. (dichloromethane) R_f0.4; ν_{max} (film) 2955s, 2930s, 2860s, 1740s (C=O,ester), 1714s (C=O,ketone), 1461m, 1437m, 1411m, 1380m, 1360m, 1275m, 1199s, 1167m and 1007m cm^{-1}; δH (WH 300) 0.89 (3H, t, J 7Hz, 11-CH_3), 1.14 (3H, d, J 7Hz, $CHCH_3$), 1.22-1.30 (8H, br, 7,8,9,10-CH_2), 1.54-1.61 (2H, m, 6-CH_2), 2.26-2.33, 2.75-2.83 (2H, 2x m, CH_2COOMe), 2.50-2.55 (2H, m, 5-CH_2), 2.98-3.05 (1H, m, 3-CH) and 3.66 (3H, s, OCH_3); δC (AM 250) 14.01 (q, 11-CH_3), 16.71 (q, $CHCH_3$), 22.57 (t, 10-CH_2), 23.60 (t, 9-CH_2), 29.07 (t, 8-CH_2), 29.19 (t, 7-CH_2), 31.66 (t, 6-CH_2), 36.72 (t, CH_2COOMe),

41.15 (t, 5-$\underline{C}H_2$), 42.01 (d, 3-$\underline{C}H$), 51.56 (s, O$\underline{C}H_3$), 172.69 (s, $\underline{C}$OOMe) and 212.77 (s, $\underline{C}$=O); m/e (NH_3 C.I.) 229 (MH^+, 100%), 197 (44), 144 (15) and 127 (17); m/e (E.I.) 228 (M^+, 2%), 197 (10), 144 (22), 127 (47), 112 (23), 57 (100), 43 (38) and 41 (43); M^+ (E.I.) found 228.1726; $C_{13}H_{24}O_3$ requires 228.1725.

Preparation of (±)-3,5-dimethyl-4-oxohexanoic acid (4c)

The general proceedure for Michael additions was followed using isobutyraldehyde t-butylhydrazone (1c) and methyl crotonate. The crude hydrazone-ester was hydrolysed (method B , work up D) and the ketoacid purified by column chromatography (50g silica, eluant ether) yield 1.012g. further purification of a sample (370mg) by p.l.c. (4 plates, eluant ether:dichloromethane; 3:1) gave the title ketoacid (4c) (140mg, 47%); t.l.c. (ether:dichloromethane; 3:1) R_f0.5; ν_{max} (film) 3700-2400m br (O-H), 2980s, 2940m, 2880m, 1715s (C=O,ketone), 1705s (C=O,acid), 1469m, 1402m, 1386m, 1369m, 1276m, 1230m, 1178m, 1150m, 1099 and 1027m cm^{-1}; δ_H (WH 300) 1.09-1.16 (9H, m, 3x $C\underline{H}_3$), 2.30-2.37, 2.78-2.86 (2H, 2x m, 2-$C\underline{H}_2$), 2.81-2.88 (1H, m, 5-C$\underline{H}$), 3.12-3.20 (1H, m, 3-C$\underline{H}$) and 9.85-10.16 (1H, br, COO$\underline{H}$); δC (AM 250) 16.92, 18.07, 18.74, (3x q, 3x $\underline{C}H_3$), 36.83 (t, 2-$\underline{C}H_2$), 39.16, 40.21 (2x d, 3-$\underline{C}$H, 5-$\underline{C}$H), 178.12 (s, $\underline{C}$OOH) and 216.47 (s, $\underline{C}$=O); m/e (E.I.) 158 (M^+, 1%), 115 (33), 87 (22), 71 (39) and 43 (100); analysis found C:60.8, H:9.1%; $C_8H_{14}O_3$ requires C:60.7, H:8.9%.

Similarly prepared:

From benzaldehyde t-butylhydrazone (1g) and methyl crotonate:

(±)-3-Methyl-4-oxo-4-phenylbutanoic acid (4g)[95] (47%); oil; t.l.c. (acetone:ethyl acetate; 1:3) R_f0.5; ν_{max} (film) 3600-2400m br (O-H), 2975m, 2935m, 2880m, 1705s (C=O,acid), 1679s (C=O,Ar-ketone), 1597m, 1580m, 1448m, 1400m, 1382m, 1362m, 1348m, 1284m, 1242s, 1227s, 1194s, 1183s, 1076m, 1064m, 1003m, 982s, 947m, 929m, 795m, 738m, 706s and 688m cm^{-1}; δH (WH 300) 1.24 (3H, d, J 7Hz, $CHC\underline{H}_3$), 2.45-2.52, 2.96-3.04 (2H, 2x m, $C\underline{H}_2COOH$), 3.87-3.95 (1H, m, 3-C<u>H</u>), 7.44-7.60, 7.95-7.99 (5H, 2x m, Ph) and 8.40-9.10 (1H, br, COO<u>H</u>); δC (AM 250) 17.83 (q, $CH\underline{C}H_3$), 37.04 (t, $\underline{C}H_2COOH$), 37.09 (d, 3-<u>C</u>H), 128.41, 128.64, 133.08 (3x d, <u>C</u>H of Ph), 135.65 (s, $\underline{C}_{ipso}$), 178.04 (<u>C</u>OOH) and 202.41 (s, <u>C</u>=O); m/e (E.I.) 192 (M^+, 1%), 105 (100) and 77 (32); M^+ (E.I.) found: 192.0786; $C_{11}H_{12}O_3$ requires: 192.0786.

General Procedure for Ene Reactions of t-Butylhydrazones

A solution of t-butylhydrazone (5.0mmol) and methyl acrylate (10mmol) or acrylonitrile (15mmol) was heated in xylene or toluene (10ml) under reflux in an inert atmosphere for 24h. The solvent and excess enophile were removed by concentration to give the crude azo compound. The azo compound was tautomerised to the hydrazone with TFA (2ml) under an inert atmosphere for 80-300min. Hydrolysis (method A, work up D or F) gave the crude product.

Preparation of Methyl 4-oxopentanoate (6a)

The general procedure was followed using acetaldehyde t-butylhydrazone (1a) and methyl acrylate in toluene. The crude ketoester was purified by column chromatography (50g silica, eluant ether:dichloromethane; 1:24) yield 0.560g. Further purification of a sample (225mg) by p.l.c. (3 plates, eluant ether:dichloromethane; 3:197) gave the title ketoester[148] (6a) (188mg, 80%); t.l.c. (ether:dichloromethane; 1:39) R_f0.2; ν_{max} (film) 3010w, 2960m, 2930w, 2855w, 1738s (C=O,ester), 1716s (C=O,ketone), 1440m, 1410m, 1362m, 1318m, 1268m, 1214m and 1162s cm^{-1}; δH (AM 250) 2.21 (3H, s, 5-C$\underline{H}_3$), 2.57-2.62 (2H, m, 2-C$\underline{H}_2$), 2.75-2.80 (2H, m, 3-C$\underline{H}_2$) and 3.69 (3H, s, OC$\underline{H}_3$); δC (AM 250) 27.66 (t, 2-$\underline{C}H_2$), 29.66 (q, 5-$\underline{C}H_3$), 37.83 (t, 3-$\underline{C}H_2$), 51.59 (q, O$\underline{C}H_3$), 172.98 (s, $\underline{C}$OOMe) and 206.30 (s, $\underline{C}$=O); m/e (E.I.) 130 (M^+, 3%), 115 (23), 99 (29) and 43 (100); analysis found C:55.2, H:7.6%; $C_6H_{10}O_3$ requires C:55.4, H:7.7%.

Similarly prepared:

From isobutyraldehyde t-butylhydrazone (1c) and methyl acrylate in xylene:

Methyl 5-methyl-4-oxohexanoate[149] (6c) (77%); t.l.c. (ether:dichloromethane; 1:19) R_f0.5; ν_{max} (film) 2980s, 2935m, 2885m, 1744s (C=O,ester), 1716s (C=O,ketone), 1470m, 1443m, 1414m, 1386m, 1369m, 1362m, 1209s, 1169s, 1093m, 1076m and 1025m cm^{-1}; δH (WH 300) 1.13 (6H, d, $\underline{J}$ 7Hz, CH(C$\underline{H}_3$)$_2$), 2.65 (1H, septet, $\underline{J}$ 7Hz, C$\underline{H}$Me$_2$), 2.57-2.60 (2H, m, 2-C$\underline{H}_2$), 2.76-2.80 (2H, m, 3-C$\underline{H}_2$) and 3.68 (3H, s, OC$\underline{H}_3$); δC (AM 250) 18.16 (q, CH(C$\underline{H}_3$)$_2$), 27.71 (t, 2-$\underline{C}H_2$), 34.69

(t, 3-$\underline{C}H_2$), 40.76 (d, 5-$\underline{C}H$), 51.63 (q, O$\underline{C}H_3$), 173.22 (s, $\underline{C}$OOMe) and 212.45 (s, C=O); m/e (NH_3 C.I.) 176 (MNH_4^+, 95%) and 159 (MH^+, 100); m/e (E.I.) 127 (21%), 115 (100), 87 (16), 71 (13), 59 (17), 55 (41) and 43 (42); analysis found C:60.7, H:9.0%; $C_8H_{14}O_3$ requires C:60.7, H:8.9%.

From pentanal $\underline{t}$-butylhydrazone (1d) and methyl acrylate in xylene:

Methyl 4-oxooctanoate[150] (6d) (74%); t.l.c. (dichloromethane) R_f0.2; ν_{max} (film) 2965s, 2940s, 2880m, 1742s (C=O,ester), 1717s (C=O,ketone), 1464m, 1442m, 1412m, 1361m, 1204s, 1169m, 1130m and 1097m cm^{-1}; δH (WH 300) 0.91 (3H, t, $\underline{J}$ 7Hz, 8-C$\underline{H}_3$), 1.32 (2H, $\underline{ca}$ sextet, $\underline{J}$ 8Hz, 7-C$\underline{H}_2$), 1.56 (2H, $\underline{ca}$ pentet, $\underline{J}$ 7Hz, 6-C$\underline{H}_2$), 2.45 (2H, t, $\underline{J}$ 8Hz, 5-C$\underline{H}_2$), 2.57-2.61 (2H, m, 2-C$\underline{H}_2$), 2.71-2.76 (2H, m, 3-C$\underline{H}_2$) and 3.77 (3H, s, OC$\underline{H}_3$); δC (AM 250) 13.75 (q, 8-$\underline{C}H_3$), 22.25 (t, 7-$\underline{C}H_2$), 25.87 (t, 6-$\underline{C}H_2$), 27.69 (t, 2-$\underline{C}H_2$), 36.98, 42.45 (2x t, 5-$\underline{C}H_2$,3-$\underline{C}H_2$), 51.65 (q, O$\underline{C}H_3$), 173.19 (s, $\underline{C}$OOMe) and 208.92 (s, $\underline{C}$=O); m/e (NH_3 C.I.) 190 (MNH_4^+, 33%), 173 (MH^+, 100), 158 (13) and 141 (11); analysis found C:63.1, H:9.5%; $C_9H_{16}O_3$ requires C:62.8, H:9.4%.

From octanal $\underline{t}$-butylhydrazone (1f) and methyl acrylate in xylene:

Methyl 4-oxoundecanoate (6f) (89%); t.l.c. (dichloromethane) R_f0.2; ν_{max} (film) 2965s, 2930s, 2860m, 1743s (C=O,ester), 1716 (C=O,ketone), 1464m, 1455m, 1436m, 1412m, 1361m, 1206m and 1176m cm^{-1}; δH (WH 300) 0.88 (3H, t, $\underline{J}$ 7Hz, 11-C$\underline{H}_3$), 1.23-1.33 (8H, br, 10,9,8,7-C$\underline{H}_2$), 1.56-1.63

(2H, m, 6-C$\underline{H}_2$), 2.45 (2H, t, $\underline{J}$ 8Hz, 5-C$\underline{H}_2$), 2.56-2.61 (2H, m, 2-C$\underline{H}_2$), 2.71-2.75 (2H, m, 3-C$\underline{H}_2$) and 3.73 (3H, s, OC$\underline{H}_3$); δC (AM 250) 13.97 (q, 11-$\underline{C}H_3$), 22.54, 23.78, 27.69, 28.90, 29.10, 31.60, 36.96, 42.74 (8x t, 8x $\underline{C}H_2$), 173.16 (s, $\underline{C}$OOMe) and 208.92 (s, $\underline{C}$=O); m/e (NH_3 C.I.) 232 (MNH_4^+, 7%), 215 (MH^+, 100), 200 (16) and 183 (33); analysis found C:67.2, H:10.4%; $C_{12}H_{22}O_3$ requires C:67.3, H:10.3%.

From pentanal $\underline{t}$-butylhydrazone (1d) and acrylonitrile in xylene, without tautomerisation or hydrolysis:

$\underline{(\pm)}$ $\underline{4\text{-(t-Butylazo)octanitrile}}$ (5d) (58%); t.l.c. (ether: petroleum; 1:3) R_f0.3; ν_{max} (film) 2965s, 2935s, 2875m, 2255w (C≡N), 1468m, 1454m, 1427m, 1365m and 1211m cm^{-1}; δH (WH 300) 0.87 (3H, t, $\underline{J}$ 8Hz, 8-C$\underline{H}_3$), 1.19 (9H, s, C(C$\underline{H}_3$)$_3$), 1.13-1.30 (4H, m, 7,6-C$\underline{H}_2$), 1.55-1.66,1.72-1.84, 1.93-2.04, 2.13-2.25 (1H+1H+1H+3H, 4x m, 5-C$\underline{H}_2$,3-C$\underline{H}_2$,2-C$\underline{H}_2$) and 3.29-3.37 (1H, m, 4-C$\underline{H}$); δC (AM 250) 13.84 (q, 8-$\underline{C}H_3$), 13.92 (t, 2-$\underline{C}H_2$), 22.39, 27.72, 28.98, 32.60 (4x t, 7,6,5,3-$\underline{C}H_2$), 26.89 (q, C($\underline{C}H_3$)$_3$), 67.35 (s, $\underline{C}$Me$_3$), 75.12 (d, 4-$\underline{C}$H) and 119.35 (s, C N); m/e (NH_3 C.I.) 210 (MH^+, 100%); analysis found C:69.1, H:11.1, N:20.3%; $C_{12}H_{23}N_3$ requires C:68.9, H:11.1, N:20.1%.

From isobutyraldehyde $\underline{t}$-butylhydrazone (1c) and acrylonitrile in xylene:

$\underline{5\text{-Methyl-4-oxohexanitrile}}$ (7c)[151] (18%); t.l.c. (dichloromethane) R_f0.4; ν_{max} (film) 2980s, 2940m, 2885m, 2255m (C N), 1714s (C=O), 1471m, 1416m, 1386m, 1368m, 1078m and 1007m cm^{-1}; δH (WH 300) 1.15 (6H, d, $\underline{J}$ 7Hz, CH(C$\underline{H}_3$)$_2$), 2.57-2.62, 2.83-2.88 (4H, 2x m, 2,3-C$\underline{H}_2$) and 2.62 (1H,

septet, J 7Hz, 5-CH); δC (AM 250) 11.54 (t, 2-$\underline{C}H_2$), 18.08 (q, CH($\underline{C}H_3$)$_2$), 35.48 (t, 3-$\underline{C}H_2$), 40.69 (d, 5-$\underline{C}$H), 119.02 (s, $\underline{C}$ N) and 209.77 (s, $\underline{C}$=O); m/e (E.I.) 125 (M^+, 9%), 82 (44), 71 (47), 55 (39), 54 (32) and 43 (100).

From pentanal t-butylhydrazone (1d) and acrylonitrile in xylene:

4-Oxooctanitrile (7d)[152] (55%); t.l.c. (dichloromethane) R_f0.3; ν_{max} (film) 2960s, 2940s, 2880m, 2250m (C≡N), 1715s (C=O), 1461m, 1414m, 1379m, 1127m and 1076m cm^{-1}; δH (WH 300) 0.88 (3H, t, J 7Hz, 8-$\underline{C}H_3$), 1.29 (2H, ca sextet, J 8Hz, 7-$\underline{C}H_2$), 1.56 (2H, ca pentet, J 8Hz, 6-$\underline{C}H_2$), 2.43 (2H, t, J 8Hz, 5-$\underline{C}H_2$) and 2.53-2.58, 2.75-2.80 (4H, 2x m, 2,3-$\underline{C}H_2$); δC (AM 250) 11.30 (t, 2-$\underline{C}H_2$), 13.66 (q, 8-$\underline{C}H_3$), 22.16, 25.70, 37.59, 42.13 (4x t, 7,6,5,3-$\underline{C}H_2$), 118.94 (s, $\underline{C}$≡N) and 206.15 (s,$\underline{C}$=O); m/e (NH_3 C.I.) 157 (MNH_4^+, 100%), 140 (MH^+, 2), 85 (9) and 69 (15); analysis found C:69.0, H:9.2, N:9.9%; $C_8H_{13}NO$ requires C:69.0, H:9.4, N:10.1%.

From octanal t-butylhydrazone (1f) and acrylonitrile in xylene:

4-Oxoundecanitrile (7f)[152] (75%); t.l.c. (dichloromethane) R_f0.3; ν_{max} (film) 2960m, 2930s, 2860m, 2255w (C≡N), 1721s (C=O), 1470m, 1416m, 1380m and 1189m cm^{-1}; δH (WH 300) 0.89 (3H, t, J 7Hz, 11-$\underline{C}H_3$), 1.23-1.34 (8H, br, 10,9,8,7-$\underline{C}H_2$), 1.56-1.63 (2H, m, 6-$\underline{C}H_2$), 2.45 (2H, t, J 8Hz, 5-$\underline{C}H_2$) and 2.56-2.61, 2.78-2.82 (4H, 2x m, 2,3-$\underline{C}H_2$); δC (AM 250) 11.31 (t, 2-$\underline{C}H_2$), 13.96 (q, 11-$\underline{C}H_3$), 22.51, 23.63, 28.92, 29.01, 31.54, 37.59, 42.43 (7x t, 10,9,8,7,6,5,3-$\underline{C}H_2$), 118.97 (s,

C≡N) and 206.21 (s, C=O); m/e (NH_3 C.I.) 199 (MH^+, 100%); m/e (E.I.) 127 (26), 110 (14), 98 (22), 97 (22), 84 (14), 82 (35), 69 (65), 57 (100), 56 (13), 55 (28), 54 (45), 43 (58), 42 (17), 41 (62) and 39 (24); analysis found C:72.9, H:10.2, N:7.6%; $C_{11}H_{19}NO$ requires C:72.9, H:10.6, N:7.7%.

Preparation of 1-Phenylpentane-1,4-dione (8a)

Acetaldehyde t-butylhydrazone (1a) (1.16g, 10mmol) and acrylonitrile (2ml, 30mmol) were heated under reflux in toluene (20ml) for 24h. The toluene and excess acrylonitrile were removed and the crude azonitrile added to phenyl magnesium bromide[153] (25mmol) in ether (40ml). The reaction was stirred at room temperature for 2h. then refluxed for 2.5h. Ammonium chloride solution (saturated, 30ml) was added to quench the reaction, the layers separated, the aqueous layer extracted with ether (2x 25ml), the combined ether layers washed with brine (30ml), dried (sodium sulphate), filtered and concentrated. Standard TFA isomerisation and hydrolysis (method A, 3.5h., work up F) were followed by column chromatography (70g silica, eluant (i) dichloromethane (200ml), (ii) dichloromethane:ether; 19:1 (400ml)) to give 0.488g crude diketone. Purification of a sample (169mg) by p.l.c. (2 plates, eluant dichloromethane:ether; 49:1) gave the title diketone[154] (8a) (131mg, 23%); t.l.c. (dichloromethane:ether;19:1) R_f0.4; δH (WH 300) 2.27 (3H, s, 5-CH_3), 2.90 (2H, t, J 6Hz, 3-CH_2), 3.29 (2H, t, J 6Hz, 2-CH_2), 7.42-7.60 and 7.96-8.03 (5H,2x m, Ph).

Preparation of 4-t-Butylazooctanitrile (5d) by Cuprate Methodology

To a solution of pentanal t-butylhydrazone (1d) (1.562g, 10.0mmol) in THF (15ml) at 0° under dry argon was added n-butyl lithium (10.5mmol) and the reaction was stirred for 10 min.. The solution was cooled to -78°, the flask containing the solution was evacuated and then re-filled with dry argon four times. The solution of the hydrazone anion was cannulated into a similarly evacuated and filled flask at -78° containing dried cuprous cyanide (0.45g, 5mmol) under argon. The solution was warmed to 0° and stirred for 30 min. to give a homogeneous green-black solution. This solution was cooled to -78° and acrylonitrile (0.7ml, 10mmol) was added. The flask was allowed to warm to ca -55° and stirred for 2h.. Acetic acid (0.5ml) was added, the solution warmed to room temperature, ether (30ml) and aqueous sodium hydroxide (2M, 15ml) were added, the layers separated and the aqueous layer extracted with ether (2x 20ml). The organic layers were combined, dried (sodium sulphate), filtered and concentrated. Column chromatography (50g silica, eluant ether:petroleum 1:9-1:4) and p.l.c. (2 plates, ether:petroleum 3:17) gave the title azonitrile (5d) (84mg, 4% based on starting hydrazone) identical to previously prepared material.

Preparation of 3-Methyl-1-phenyl-2-t-butylazobut-1-ene (9c)

Isobutyraldehyde t-butylhydrazone (1c) (10.0mmol) was

dissolved in THF (15ml) at 0°. n-Butyl lithium (11.0mmol) was added, the solution stirred for 10min., and benzaldehyde (12.0mmol) added. After 15 min. n-butyl lithium was added. After 1h. phosgene (13mmol, solution in toluene, method A) or thionyl chloride (13mmol, method B) was added and the solution warmed to room temperature over 16h. Water (0.5ml) and ether (30ml) were added, the solution dried (sodium sulphate), filtered and concentrated. Column chromatography (70g silica, eluant i ether: petroleum; 1:19, ii ether: petroleum 1:9) gave partially purified azoalkene (9c) (A:2.123g; B:1.836g). Purification of a sample (A:193mg; B:169mg) by p.l.c. (2 plates eluant ether: petroleum; 1:9) gave the title azoalkene (9c) (A:147mg, 65%; B:164mg, 74%) as a mixture of isomers (E:Z ~1:8.5, but the proportion of Z isomer increased with time); t.l.c. (ether: petroleum; 1:4) R_f 0.7 (E), 0.6 (Z); ν_{max} (film) 3085w, 3030w, 2965s, 2930m, 2910m, 2870m, 1470m, 1455m, 1447m, 1386m, 1362m, 1220m, 1210m, 757m, and 696s cm^{-1}; λ_{max} 286 nm (ϵ 8.5x 10^3); δH 1.12, 1.24 (6H, 2x d, J 7Hz, E, Z $CH(C\underline{H}_3)_2$), 1.30, 1.32 (9H, 2x s, E, Z $C(C\underline{H}_3)_3$), 3.17, 3.33 (1H, 2x septet, J 7Hz, $C\underline{H}Me_2$), 6.30, 6.63 (1H, 2x s, E, Z C=C$\underline{H}$), 7.23-7.41 and 7.66-7.69 (5H, 2x m, Ph); m/e (E.I.) 230 (M^+, 4%), 145 (100), 117 (36), 105 (24), 91 (52), 57 (64) and 41 (21); analysis found C:77.9, H:9.8, N:12.4%; $C_{15}H_{22}N_2$ requires C:78.2, H:9.6, N:12.2%.

In an n.O.e. experiment irradiation of the vinylic

hydrogen of the major isomer δH 6.63 gave n.O.e. of the major C<u>H</u>Me_2, δH 3.17 (1.5%), whereas irradiation of the vinylic hydrogen of the minor isomer δH 6.30 gave n.O.e. of the minor C<u>H</u>Me_2, δH 3.33 (0.2%).

<u>Azoalkene Reductions</u>

The reduction of 2-<u>t</u>-butylazo-3-methyl-1-phenylbut-1-ene (9c) is typical:

Azoalkene (9c) (254mg, 1.0mmol) was dissolved in glacial acetic acid (10ml) and zinc dust (300mg, 5.0mmol) was added. The solution refluxed for 3h., filtered through celite and concentrated. Column chromatography (50g silica, eluant petroleum: dichloromethane; 3:1) gave <u>3-methyl-1-phenylbutan-2-one</u> (10c) (89mg, 49%); t.l.c. (petroleum: dichloromethane; 3:1) R_f0.2; ν_{max} (film) 3090w, 3065w, 3035m, 2970s, 2935s, 2880m, 1713s (C=O), 1495m, 1467m, 1454m, 1475m, 1468m, 1259m, 1044m, 735m and 701s cm^{-1}; δH (WH 300) 1.11 (6H, d, <u>J</u> 7Hz,CH(C<u>H</u>$_3)_2$), 2.74 (1H, septet, <u>J</u> 7Hz, C<u>H</u>Me_2), 3.75 (2H, s, PhC<u>H</u>$_2$) and 7.20-7.36 (5H, m, Ph); identical to an authentic sample.[155]

<u>Similarly prepared:</u>

From 1-phenyl-2-<u>t</u>-butylazoprop-1-ene (9a)[56]:

<u>Phenylacetone</u> (10a) (55%) t.l.c. (petroleum: ether; 3:2) R_f0.4; ν_{max} (film) 3085w, 3060w, 3030w, 3000w, 2960w, 2915w, 1713s (C=O), 1603w, 1494m, 1455m, 1417m, 1368m, 1228m, 1108m, 734s and 699s cm^{-1}; δH (R 24) 2.15 (3H, s, C<u>H</u>$_3$), 3.66 (2H, s, C<u>H</u>$_2$) and 7.22 (5H, s, Ph); identical to authentic sample ex Fluka A.G..

Reduction of 2-t-butylazo-3-methyl-1-phenylbut-1-ene (9c) under similar conditions but with acetic acid: acetic anhydride (1:1) as solvent gave a different product. The crude product was dissolved in ether (20ml) and washed with sodium bicarbonate solution (saturated, 15ml), dried (sodium sulphate), filtered and concentrated. Column chromatography (60g silica, eluant ethyl acetate: dichloromethane; 3:17-3:7) followed by p.l.c. (1 plate, eluant ethyl acetate: dichloromethane; 3:17) gave (±)-2-Acetyl-5-methyl-3-isopropyl-3-benzyl-2,3-dihydro-4-oxa-1,2-diazole (11c) ν_{max} (film) 3200w, 3090w, 3070w, 3035m, 2975s, 2940s, 2885m, 1668s (C=O, amide), 1497m, 1454s, 1423s, 1381s, 1557m, 1346m, 1316m, 1280s, 1218m, 1205m, 741m and 705m cm^{-1}; δH (WH 300) 0.91, 1.15 (6H, 2x d, J 7Hz, $CH(C\underline{H}_3)C\underline{H}_3$), 1.75 (3H, s, $O\text{-}C(C\underline{H}_3)=N$), 2.06 (3H, s, $C\underline{H}_3CON$), 2.95 (1H, ca septet, J 7Hz, $C\underline{H}MeMe$), 3.14, 3.58 (2H, ABq, J 14Hz, $PhC\underline{H}_2$) and 7.15-7.33 (5H, m, Ph); δC (AM 250) 10.90 (q, $O\text{-}C(\underline{C}H_3)=N$), 16.36, 16.66 (2x q, $CH(\underline{C}H_3)\underline{C}H_3$), 22.26 (q, $\underline{C}H_3ON$), 33.21 (d, $\underline{C}HMe_2$), 38.78 (t, $\underline{C}H_2Ph$), 106.38 ($O\text{-}\underline{C}(CH_2Ph)(CHMe_2)\text{-}N$), 126.90, 127.90, 130.37 (3x d, $\underline{C}H$ of Ph), 135.13 (s, $\underline{C}_{ipso}$), 154.81 (s, O-$\underline{C}Me=N$) and 166.59 (s $Me\underline{C}ON$); m/e (NH_3 C.I.) 277 (MNH_4^+, 2%), 261 (MH^+, 100), 169 (37), 127 (72) and 91 (10); m/e (E.I.) 260 (M^+, 3%), 259 (17), 185 (30), 175 (16), 169 (11), 149 (13), 129 (24), 127 (100), 91 (17), 57 (30), 43 (56) and 41 (26); M^+ (E.I.) found: 260.1525; $C_{15}H_{20}N_2O_2$ requires 260.1525.

Experiments Described In Chapter 3

Preparation of Tritylhydrazine Hydrochloride (20)

Trityl chloride (98.6g, 0.35mol) was added to a solution of hydrazine hydrate (120ml, excess) in THF (500ml) and the mixture heated under reflux for 16h.. After cooling the solution was concentrated to half volume and extracted with ether (1l and 200ml). The organic layer was washed with water (2x 200ml), dried (sodium sulphate) and hydrogen chloride in methanol (5.5M, 64ml, 1 equivalent) was added. The solution was allowed to stand for 24h. whilst the product crystallised. The solid was collected by filtration and washed with ether to give the title hydrazine hydrochloride (20) (99.1g, 90%); m.p. 109-112° (lit[163] 108-113°); t.l.c. (methanol) R_f0.7; δH (WH 300, CD_3OD) 7.18-7.49 (m, Ph); δC (AM 250, CD_3OD) 76.36 (s, $\underline{C}Ph_3$), 128.90, 129.58, 129.63 (3x d, $\underline{C}_{o,m,p}$) and 143.31 (s, $\underline{C}_{ipso}$); m/e (NH_3 C.I.) 243 (100%) and 165 (27); m/e (E.I.) 243 (93%), 165 (100) and 36 (27).

General Procedure for the Preparation of Tritylhydrazones (21)

The following procedure for the preparation of Acetaldehyde tritylhydrazone (21a) is typical.

Tritylhydrazine hydrochloride (20) (12.4g, 40mmol) was dissolved in methanol (200ml) and stirred vigo rously, a solution of sodium formate (4g, 60mmol) in water (60ml) was added slowly, then acetaldehyde (2.2ml, 44mmol) was added

and the solution was stirred under argon for 2 hours. The solid hydrazone was collected by filtration, washed with methanol (30ml) and petroleum (60ml) and dried under vacuum (room temperature) for 16h. to yield Acetaldehyde tritylhydrazone (21a) as a mixture of isomers (E:Z ~5:4) (6.58g, 56%); m.p.112-114°; ν_{max} (nujol) 3060w, 3030w, 1601w, 1096m, 1089m, 1063m, 1032m, 769m, 761m, 739m, 728m 704s cm^{-1}; δH (WH 300) 1.75, 1.77 (3H, 2x d, J 5Hz, CH_3), 6.70, 7.00 (1H, 2x q, J 5Hz, HC=N) and 7.22-7.40 (15H, m, Ph); δC (AM 250) 12.27, 18.00 (2x q, CH_3), 72.54, 72.58 (2x s, CPh), 126.43, 126.57, 127.61, 127.71, 128.93, 129.05 (6x d, CH of Ph), 137.79, 140.06 (2x s, C_{ipso}), 145.51 and 145.78 (2x d, HC=N); m/e (NH_3 C.I.) 301 (MH^+, 38%), 243 (100), 183 (10), 165 (18) and 59 (16).

Similarly Prepared:

Acetone tritylhydrazone (21b) (90%); m.p.119-120°; ν_{max} ($CHCl_3$) 3060w, 2960s, 2930s, 2860s, 1597m, 1487s, 1445s, 760s, 720s and 705s cm^{-1}; δH (WH 300) 1.74, 1.80 (6H, 2x s, 2x CH_3), 5.38 (1H, br, NH) and 7.19-7.46 (15H, m, Ph); δC (AM 250) 15.63 (q, CH_3), 25.30 (q, CH_3), 75.50 (s, CPh_3), 126.43, 127.60, 129.16 (3x d, CH of Ph), 145.66 and 146.17 (2x s, C_{ipso}, C=N); m/e (NH_3 C.I.) 315 (MH^+, 11%), 243 (100) and 165 (27); m/e (E.I.) 243 (100%) and 165 (60).

Pentanal tritylhydrazone (21d) (77%, as a mixture of isomers E:Z ~2:1); waxy solid; ν_{max} (nujol) 3090m, 3055m, 3030m, 3020m, 1597m, 1206m, 1187m, 1167m, 1158m, 1106m, 1083m, 1064m, 1030m, 905m, 760s, 745s, 720m and 706s cm^{-1};

δH (WH 300) 0.83, 0.96 (3H, 2x t, J 7Hz, 5-C$\underline{H}_3$), 1.10-1.64 (4H, m, 3,4-C$\underline{H}_2$), 2.14 (2H, m, 2-C$\underline{H}_2$), 6.57, 6.95 (1H, 2x t, J 6Hz, 1-C$\underline{H}$) and 7.17-7.54 (15H, m, Ph); δC (AM 250) 13.78 (q, 5-$\underline{C}H_3$), 21.83, 22.45, 25.83, 28.25, 28.94, 31.61 (6x t, 2,3,4-$\underline{C}H_2$), 72.73 (s, $\underline{C}Ph_3$), 126.43, 126.57, 127.61, 127.73, 128.96, 129.11 (6x d, $\underline{C}$H of Ph), 143.89, 144.85 (2x d, H$\underline{C}$=N), 145.52 and 145.78 (2x s, $\underline{C}_{ipso}$); m/e (NH_3 C.I.) 343 (MH^+, 10%), 259 (10) and 243 (100).

Cyclopentanone tritylhydrazone (21h); 83%; m.p. 127-130.5 with decomp.; t.l.c. (dichloromethane) R_f0.4; ν_{max} (nujol) 3070w, 3050w, 3025w, 1070m, 768m, 761m, 753m, 722m, 711m and 699s cm^{-1}; δH (WH 300) 1.62, 1.77 (4H, 2x ca pentet, J 7Hz, 3,4-C$\underline{H}_2$), 2.10, 2.23 (4H, 2x t, J 7Hz, 2,5-C$\underline{H}_2$), 5.27 (1H, br, N$\underline{H}$) and 7.19-7.48 (15H, m, Ph); δC (AM 250) 24.83 (2C, unresolved, t, 3,4-$\underline{C}H_2$), 26.54, 33.01 (2x t, 2,5-$\underline{C}H_2$), 72.65 (s, $\underline{C}Ph_3$), 126.41, 127.64, 129.05 (3x d, $\underline{C}$H of Ph), 146.04 (s, $\underline{C}_{ipso}$) and 158.66 (s, $\underline{C}$=N); m/e (NH_3 C.I.) 341 (MH^+, 20%), 243 (100) and 165 (18).

Cyclohexanone tritylhydrazone (21e) (89%); m.p. 132-134°; ν_{max} ($CHCl_3$) 3060w, 3005s, 2940s, 2830s, 1598w, 1488w and 699s cm^{-1}; δH (WH 300) 1.41-1.70 (6H, m, 3,4,5-C$\underline{H}_2$), 2.12, 2.33 (4H, 2x t, J 6Hz, 2,6-C$\underline{H}_2$), 5.60 (1H, br, N$\underline{H}$) and 7.19-7.38 (5H, m, Ph); δC (AM 250) 25.13, 25.94 (2C, unresolved), 27.19, 35.62 (4x t, $\underline{C}H_2$ of ring), 72.30 (s, $\underline{C}Ph_3$), 126.38, 127.58, 129.20 (3x d, $\underline{C}$H of Ph), 146.02 and 152.01 (2x s, $\underline{C}_{ipso}$, $\underline{C}$=N); m/e (NH_3C.I.) 355 (MH^+, 17%), 243 (100) and 165 (18); m/e (E.I.) 243 (100%) and 165 (52).

Cyclododecanone tritylhydrazone (21i) (87%); m.p.141.5-142.5°; ν_{max} ($CHCl_3$) 3060w, 3010s, 2920s, 2850s, 1564m, 1468m, 1448m, 909s and 705s cm^{-1}; δH (WH 300) 0.85-0.94, 1.15-1.60 (18H, 2x m, 3,4,5,6,7,8,9,10,11-CH_2), 2.15, 2.24 (4H, 2x t, J 7Hz, 2,12-CH_2), 5.50 (1H, br, NH), 7.16-7.29 and 7.40-7.44 (15H, 2x m, Ph); δC (AM 250) 22.40, 22.74, 23.27, 23.42, 23.53 (relative intensity 2) 24.83, 25.89, 26.30, 27.66, 31.94 (10x t, CH_2 of ring), 72.54 (s, CPh_3), 126.17, 127.52, 129.20 (3x d, CH of Ph), 146.43 and 151.14 (2x s, C_{ipso}, C=N); m/e (NH_3 C.I.) 439 (MH^+, 9%), 243 (100), 184 (20) and 165 (18).

General Procedure for the Preparation of Alkanes (22) From Tritylhydrazones (21)

To a solution of tritylhydrazone (21) (5.0mmol) in THF (30ml) at -40° was added base (methyl lithium or LDA) (5.5mmol). After 20 min. alkyl halide (6.5mmol) was added, the bath allowed to warm to -30°, and kept at -30° for 3h.. The reaction was quenched with acetic acid (5.5mmol), ethanethiol (2ml) was added and the flask allowed to warm to room temperature, during which time nitrogen was evolved. Ether (80ml) was added and the resulting solution washed with sodium hydroxide solution (2M, 2x 100ml) and brine (60ml), dried (sodium sulphate), filtered and concentrated. The product was purified by column chromatography (50g silica, eluant: petroleum). A sample was dissolved in dichloromethane (20ml), bromine was added dropwise until a brown colour persisted, the solution was

washed with sodium thiosulphate solution (saturated, 2x 15ml), dried (sodium sulphate), filtered and concentrated. P.l.c. (eluant petroleum) gave the pure alkane.

Preparation of tetradecane (22ad)

The general method was followed using acetaldehyde tritylhydrazone (21a) (1.500g, 5.0mmol), LDA as base, and 1-iodododecane as the electrophile to yield crude (22ad) (1.397g). Purification of a sample (352mg) by bromination and p.l.c. (4 plates) gave tetradecane[156] (22ad) (68mg, 27%) ; g.c. retention time: 3.8min./154.5°; ν_{max} 2960s, 2935s, 2920s, 2855s, 1467m and 1380m cm^{-1}; δH (WH 300) 0.89 (6H, t, J 7Hz, $C\underline{H}_3$), and 1.24-1.30 (24H, br, all $C\underline{H}_2$); δC (AM 250) 14.13 (q, $\underline{C}H_3$), 22.74, 29.40, 29.74 (relative intensity 3) and 31.98 (4x t, all $\underline{C}H_2$); m/e (E.I.) 198 (M^+, 2%), 169 (1), 155 (2), 141 (3), 127 (4), 113 (5), 99 (8), 85 (37), 71 (61), 57 (100), 43 (91) and 41 (36); analysis found C:85.2, H:15.4%; $C_{14}H_{30}$ requires C:84.8, H:15.2%.

Similarly Prepared:

From acetone tritylhydrazone (21b), LDA and 1-iodododecane:

2-Methyltetradecane (22bd) (38%); g.c. retention time 6.1min./151°; ν_{max} (film) 2960s, 2925s, 2860s, 1467m, 1385w and 1368w cm^{-1}; δH (WH 300) 0.87 (6H, d, J 7Hz, $CH(C\underline{H}_3)_2$), 0.89 (3H, t, J 7Hz, $CH_2C\underline{H}_3$), 1.25-1.29 (22H, br, all $C\underline{H}_2$), and 1.43-1.63 (1H, m, $C\underline{H}Me_2$); δC (AM 250) 14.07 (q, 14-$\underline{C}H_3$), 22.64 (q, relative intensity 2, $CH(\underline{C}H_3)_2$), 22.69, 27.42, 27.98, 29.36, 29.66, 29.70 (relative intensity 3), 29.73, 29.96, 31.93 (11x t, all $\underline{C}H_2$), and 39.09 (d, $\underline{C}HMe_2$);

m/e (E.I.) 210 (M^+, 3%), 195 (4), 168 (15), 167 (7), 105 (16), 99 (9), 85 (24), 71 (35), 57 (85), 55 (21), 43 (100) and 41 (55); analysis found C:84.8, H:15.3%; $C_{15}H_{32}$ requires C:84.8, H:15.2%.

From pentanal tritylhydrazone (21d), LDA and 1-iodododecane:

Heptadecane[157] (22dd) (46%); g.c. retention time 15.8min./154.5°; ν_{max} (film) 2960s, 2920s, 2850s, 1467m, 1464m and 1380m cm^{-1}; δH (WH 300) 0.89 (6H, t, J 7Hz, C$\underline{H}_3$) and 1.24-1.29 (30H, br, all C$\underline{H}_2$); δC (AM 250) 14.19 ($\underline{C}H_3$), 22.79, 29.47, 28.81 (relative intensity 4.5) and 32.04 (all $\underline{C}H_2$); m/e (E.I.) 240 (M^+, 3%), 183 (2), 169 (2), 155 (3), 141 (3), 127 (4), 113 (6), 99 (10), 85 (40), 71 (60), 57 (100), 43 (78) and 41(27); analysis found C:85.2, H:14.8%, $C_{17}H_{36}$ requires C:84.9, H:15.1%.

From cyclopentanone tritylhydrazone (21h), LDA and 1-iodododecane:

Dodecylcyclopentane (22hd) (27%); g.c. retention time 29.9min./151°; ν_{max} (film) 2955s, 2920s, 2855s, 1467m and 1380w cm^{-1}; δH (WH 300) 0.89 (3H, t, J 7Hz, C$\underline{H}_3$), 1.00-1.77 (31H, br m, all C$\underline{H}_2$ and C$\underline{H}$); δC 14.16 ($\underline{C}H_3$), 22.76, 25.99 (relative intensity 2), 28.89, 29.44, 29.74 (relative intensity 2), 29.78 (relative intensity 3), 29.81, 30.05, 32.01, 32.84, 36.36 (all $\underline{C}H_2$) and 40.29 ($\underline{C}$H); m/e (E.I.) 238 (M^+, 12%), 111 (8), 97 (24), 83 (47), 69 (80), 68 (71), 57 (45), 55 (70), 41 (76) and 39 (100); analysis found C:85.4, H:14.1%, $C_{17}H_{34}$ requires C:85.6, H:14.4%.

From cyclohexanone tritylhydrazone (21e), methyl lithium and benzyl bromide:

Benzylcyclohexane (22ea) (69%); g.c. retention time 5.6min./155°; ν_{max} (film) 3090w, 3065w, 3025w, 2925s, 2855s, 1607w, 1496w, 1450m, 743m and 698m cm^{-1}; δH (WH 300) 0.98-1.73 (11H, m, c-C_6H_{11}), 2.51 (2H, d, J 7Hz, CH_2Ph) and 7.11-7.37 (5H, m, Ph); δC (AM 250) 26.33, 26.60, 33.17 (3x t, CH_2 of ring), 39.78 (d, CH), 44.14 (t, CH_2Ph), 125.52, 127.99, 129.14 (3x d, CH of Ph) and 141.33 (s, C_{ipso}); m/e (E.I.) 174 (M^+, 24%), 92 (100), 91 (39), 83 (40), 82 (12), 67 (12), 65 (11), 55 (60) and 41 (24); analysis found C:89.4, H:10.2%, $C_{13}H_{18}$ requires C:89.6, H:10.4%.

From cyclohexanone tritylhydrazone (21e), methyl lithium and 1-iodobutane:

Butylcyclohexane (22ec) (39%, based on integration of g.c. trace (retention time 8.1min./100°) of isolated alkanes); ν_{max} (film) 2960s, 2930s, 2860s, 1464m, 1454m, 1449m and 1378m cm^{-1}; δH (WH 300) 0.89 (3H, t, J 7Hz, CH_3) and 1.18-1.71 (17H, m, all other H); δC (AM 250) 14.16 (q, CH_3), 23.07, 25.52, 26.83, 29.19, 33.53, 37.27 (6x t, all CH_2) and 37.73 (d, CH); m/e (E.I.) 140 (M^+, 15%), 83 (77), 82 (57), 67 (28), 55 (100), 41 (76) and 39 (36); M^+ found: 140.1565, $C_{10}H_{20}$ requires: 140.1565.

From cyclohexanone tritylhydrazone (21e), methyl lithium and 1-iodoheptane:

Heptylcyclohexane (22ec) (69%, based on integration of g.c. trace (retention time 10.7 min./123°) of isolated alkanes); ν_{max} (film) 2960s, 2925s, 2855s, 1466m, 1451m and 1382w cm^{-1}

; δH (WH 300) 0.89 (3H, t, J 7Hz, C$\underline{H}_3$), 1.15-1.34, 1.58-1.72 (23H, 2x m, all C$\underline{H}_2$ and C$\underline{H}$); δC (AM 250) 14.13 (q, $\underline{C}H_3$), 22.74, 26.52, 26.84, 26.95, 29.44, 30.04, 31.98, 33.54, 37.62 (9x t, all $\underline{C}H_2$) and 37.77 (d, $\underline{C}H$): m/e (E.I.) 182 (M^+, 10%), 83 (100), 82 (73), 57 (34), 55 (68), 43 (50) and 41 (64); M^+ found: 182.2033, $C_{13}H_{26}$ requires: 182.2034.

From cyclododecanone tritylhydrazone (21i), methyl lithium and benzyl bromide:

Benzylcyclododecane (22ia) (45%); g.c. retention time 24.5min./189°; ν_{max} (film) 3090w, 3070w, 3030m, 2935s, 2910s, 2865s, 2860s, 1605w, 1495w, 1470m, 1454m, 1447m, 729m and 701m cm^{-1}; δH (WH 300) 1.26-1.42 (23H, br m, $\underline{c}$-$C_{12}\underline{H}_{23}$), 2.54 (2H, d, J 7Hz, C$\underline{H}_2$Ph) and 7.15-7.32 (5H, m, Ph); δC (AM 250) 21.75, 23.36, 23.45, 24.30, 24.86, 28.78 (6x t, $\underline{C}H_2$ of ring), 36.32 (d, $\underline{C}HCH_2Ph$), 41.63 (t, $\underline{C}H_2Ph$), 125.48, 128.04, 129.08 (3x d, $\underline{C}H$ of Ph) and 141.87 (s, $\underline{C}_{ipso}$); m/e (E.I.) 258 (M^+, 25%), 166 (89), 111 (35), 97 (66), 92 (46) 91 (100), 83 (60), 69 (48), 55 (53) and 41 (36); analysis found C:88.6, H:11.9%; $C_{19}H_{30}$ requires C:88.3, H:11.7%.

From cyclododecanone tritylhydrazone (21i), methyl lithium and 1-iodobutane:

Butylcyclododecane (22ib) (51% by integration of g.c. trace (retention time 12.3 min./160°) of isolated alkanes); ν_{max} (film) 2960s, 2930s, 2860s, 1472m, 1449m and 1380w cm^{-1}; δH (WH 300) 0.90 (3H, t, J 7Hz, C$\underline{H}_3$) and 1.23-1.36 (29H, m, all C$\underline{H}_2$ and C$\underline{H}$); δC (AM 250) 14.16 (q, $\underline{C}H_3$), 21.81, 23.10,

23.44, 24.25, 24.91, 29.20, 29.71, 34.82 (8x t, all $\underline{C}H_2$) and 33.98 (d, $\underline{C}H$); m/e (E.I.) 224 (M^+, 19%), 125 (18), 111 (36), 97 (67), 96 (18), 83 (82), 82 (34), 69 (80), 68 (23), 67 (18), 57 (65), 55 (100), 43 (67) and 41 (72); M^+ (E.I.) found: 224 2505; $C_{16}H_{32}$ requires 224.2504.

Alkylation of a Tritylhydrazone (21) followed by radical decomposition in the absence of ethanethiol

The general procedure for alkane synthesis was followed using cyclohexanone tritylhydrazone (21e) (1.783g, 5.0mmol), n-butyl lithium and benzyl bromide, except that ethanethiol was not added to the reaction before it was warmed to room tenperature. Column chromatography (60g silica, eluant petroleum) gave a crude product (1.125g). Purification of a sample (283mg) by p.l.c. (3 plates, eluant petroleum) gave a mixture of benzylidene cyclohexane[158] and 1-benzylcyclohexene (23) in a ratio of approximately 1:4; 19mg (combined yield), 9%; δH (WH 300) 1.53-1.67 (m, all non-allylic $C\underline{H}_2$), 1.85-1.91, 2.01-2.05 (2x m, $C\underline{H}_2CH=C\underline{H}_2$), 2.28, 2.40 (2x ca t, J 5Hz, $C\underline{H}_2C(=C)C\underline{H}_2$), 3.27 (s, $PhC\underline{H}_2$), 5.47-5.55 (m, $CH_2C\underline{H}=C$), 6.23-6.26 (m, $PhC\underline{H}=$) and 7.17-7.35 (m, Ph); m/e (E.I.) 172 (M^+, 84%), 143 (8), 129 (23), 115 (14) 104 (10), 91 (48), 81 (100) and 80 (28).

Preparation of 1-Butyl-1-t-butylazocyclohexane (12eb)

The general procedure for the alkylation of trityl-hydrazones was followed using cyclohexanone t-butyl-

hydrazone (1e) (0.864g, 5.0mmol), n-butyl lithium and 1-iodobutane. Ethanethiol was not added prior to warming to room temperature. Column chromatography (50g silica, eluant petroleum) gave the title compound (12eb) (0.826g, 74%); t.l.c. (petroleum) R_f0.3; ν_{max} (film) 2975s, 2930s, 2865s, 1452s, 1388m, 1382m, 1362m, 1229m, 1210m and 738m cm^{-1}; δH (WH 300) 0.85 (3H, t, J 7Hz, $C\underline{H}_3$), 1.01-1.51, 1.88-1.93 (16H, 2x m, 8x $C\underline{H}_2$) and 1.19 (9H, s, $C(C\underline{H}_3)_3$); δC (AM 250) 14.00 (q, $\underline{C}H_3$), 22.27, 23.42, 24.80, 26.21, 34.04, 38.57 (6x t, all $\underline{C}H_2$), 26.92 (q, $C(\underline{C}H_3)_3$), 66.48 and 69.12 (2x s, $\underline{C}$-N=N-$\underline{C}Me_3$); m/e (NH_3 C.I.) 225 (MH^+, 100%) and 35 (93).

Experiments Described in Chapter 4

General Procedure For The Preparation Of BOC Hydrazines

The following method is typical:

Preparation of BOC Isopropylhydrazine (30)

To a solution of t-butylcarbazate (27.35g, 0.20mol) in acetone (50ml) was added acetic acid (0.1ml) and the solution stirred for 16h.. The excess acetone was removed by concentration. The crude hydrazone was dissolved in ethanol (600ml), added to 5% platinum on carbon catalyst (820mg) and hydrogenated (atmospheric pressure) until hydrogen uptake ceased. The catalyst was removed by filtration through celite and the solution concentrated. The crude product was recrystallised from hexane to give the title hydrazine (30)[159] (32.82g, 91%); m.p.51.5-52° (lit.[159]:47-51°); ν_{max} (nujol) 3460-3140br m, 1715s (C=O), 1280m, 1254m and 1166s cm^{-1}; δ H (WH 300) 1.00 (6H, d, J 6Hz, $CH(C\underline{H}_3)_2$); 1.44 (9H, s, $C(C\underline{H}_3)_3$); 3.11 (1H, septet, J 6Hz) and 6.32 (2H, br, $N\underline{H}N\underline{H}$); m/e ($NH_3$ C.I.) 175 (MH^+, 4%), 119 (100) and 75 (40).

Similarly Prepared:

From t-butylcarbazate (24.19g, 0.20mol) and cyclohexanone (20ml, 0.20mol) in dichloromethane (50ml), recrystallised from ethanol-water:

BOC Cyclohexylhydrazine (40)[130] (37.90g, 97%); m.p. 83-85° (lit.[130]:76-78); ν_{max} (nujol) 3470s (N-H), 3250m (N-H), 3235m (N-H), 1691s (C=O), 1539m (N-H), 1391m, 1374m, 1367m,

1278m, 1252m, 1246m, 1180m, 1164m, 1113m, 1056m, 1044m, 1020m, 892m, 872m and 843m cm^{-1}; δ H (WH 300) 1.01-1.85 (10H, m, 5x $C\underline{H}_2$ of ring), 1.47 (9H, s, $C(C\underline{H}_3)_3$), 2.79 (1H, m, $C\underline{H}N$) and 6.04 (2H, br, $N\underline{H}N\underline{H}$); δ C (AM 250) 24.30, 25.98, 31.09 (3x t, $\underline{C}H_2$ of ring), 28.30 (q, $C(\underline{C}H_3)_3$), 58.40 (d, $\underline{C}HN$), 80.13 (s, $\underline{C}Me_3$) and 156.80 (s, $\underline{C}$=O); m/e (NH_3 D.C.I.) 215 (MH^+, 10%), 159 (100) and 114 (41); analysis found C: 61.5, H:10.4, N:12.9%; $C_{11}H_{22}N_2O_2$ requires C:61.7, H:10.4, N:13.1%.

Preparation of BOC 2,4-Dimethylpent-3-ylhydrazine (50)

A solution of t-butylcarbazate (70.2g, 0.53mol) and 2,4-dimethylpentan-3-one (79ml, 0.56mol) in ethanol (600ml) was refluxed for 16h. to give the BOC hydrazone. Ethanol was added to increase the total volume to 1.0l and the mixture hydrogenated catalytically (H_2 15 p.s.i./5% Pt on carbon, 2.0g/16h.) to give the title BOC hydrazine (50) (109.2g, 90%) as a crude oil. Purification of a sample (198mg) by p.l.c. (3 plates, eluant petroleum:isopropanol 9:1) gave the title BOC hydrazine (50) (99mg, 45%); as an oil; t.l.c. (hexane:isopropanol 9:1) R_f0.3; ν_{max} (film) 3205br m (N-H), 2970s, 2960s, 2930m, 2865m, 1706s (C=O), 1508m, 1471m, 1455m, 1388m, 1364m, 1274m, 1251m, 1159m, 1043m, 1010m, 872m and 772m cm^{-1}; δ H (QE 300) 0.98, 1.01 (12H, 2x d, J 7Hz, $CH(CH(C\underline{H}_3)_2)_2$), 1.47 (9H, s, $OC(C\underline{H}_3)_3$), 1.84 (2H, m, $CH(C\underline{H}Me_2)_2$), 2.43 (1H, m, $C\underline{H}iPr_2$), 6.02 and 6.43 (2H, 2x br, $N\underline{H}N\underline{H}$); m/e (E.I.) 230 ($M^+$, 0.1%), 174 (9), 131 (90), 113 (8), 99 (10), 87 (55), 70 (23), 57 (100), 43 (56) and

41 (48); M^+ (E.I.) found: 230.1984; $C_{12}H_{26}N_2O_2$ requires 230.1994.

General Procedure for the Preparation of Secondary Alkyl Hydrazones in Aqueous Solution

The following procedure is typical:

Preparation of Acetone Isopropylhydrazone (31b)

BOC isopropylhydrazine (30) (4.660g, 28mmol) was dissolved in a solution of hydrogen chloride in methanol (ca 6M, 25ml) and stirred until gas evolution ceased (ca 2h.). The solution was concentrated and the crude hydrochloride salt was dissolved in water (30ml). Sodium hydroxide pellets were added until the pH was 10-11. The solution was cooled to room temperature, acetone (2.3ml, 31mmol) added and the solution stirred under an inert atmosphere for 2h.. Ether (40ml) was added and the layers separated. The aqueous layer was extracted with ether (2x 30ml), the organic layers combined, dried (sodium sulphate), filtered and concentrated. Distillation from calcium hydride gave the title hydrazone (31b) 0.583g, 19%; b.p. 82-87°/346mmHg; δ H (WH 300) 1.14 (6H, d, J 6Hz, $CH(C\underline{H}_3)_2$), 1.74, 1.94 (6H, 2x s, $C\underline{H}_3C(=N)C\underline{H}_3$), 3.39 (1H, septet, J 6Hz, $C\underline{H}Me_2$) and 9.48 (1H, br, N<u>H</u>).

Similarly Prepared:

From BOC isopropylhydrazine and benzaldehyde:

Benzaldehyde isopropylhydrazone (31g) (18%) as a mixture of isomers E:Z ~6:1; b.p. 82°/0.09mmHg; δ H (WH 300) 1.22, 1.23 (6H, 2x d, J 6Hz, $CH(C\underline{H}_3)_2$), 3.60, 3.93 (1H, 2x

septet, J 6Hz, CHMe$_2$), 7.24-7.37, 7.55-7.58 (2x m, 5H, Ph) and 7.64 (1H, s, CH(=N)); m/e (NH_3 C.I.) 163 (MH^+, 100%) and 147 (9).

From BOC cyclohexylhydrazine and acetaldehyde:

Acetaldehyde cyclohexylhydrazone (41a) as a mixture of isomers E:Z ~7:5; (46%); b.p. 52-54°/0.9mmHg; ν_{max} (film) 3400-3100br w (N-H), 2930s, 2855s, 1453m, 1381m, 1368m and 1111m cm^{-1}; δH (WH 300) 1.00-2.00 (10H, m, 5x CH_2 of ring), 1.71, 1.85 (3H, 2x d, J 6Hz, CH_3CH=N), 3.01-3.11 (1H, m, NHCH), 4.11 (1H, br, NH), 6.61 and 7.04 (1H, 2x q, J 5Hz, MeCH=N).

From BOC cyclohexylhydrazine (40) and acetone:

Acetone cyclohexylhydrazone (41b) (23%); b.p. 101-102°/22mmHg; ν_{max} (film) 3600-3050br m, 2990m, 2940s, 2860s, 1453m, 1374m, 1362m, 1187m and 1132m cm^{-1}; δH (WH 300) 1.02-2.04 (10H, m, CH_2 of ring), 1.74, 1.93 (3H, 2x s, $CH_3C(=N)CH_3$) and 3.00-3.10 (1H, m, NHCH).

From BOC cyclohexylhydrazine and benzaldehyde:

Benzaldehyde cyclohexylhydrazone (41g) (70%); b.p. 131-135°/0.1mmHg; ν_{max} (film) 3600-3140br w (N-H), 3065m, 3025m, 2930m, 2855m, 1598m, 1568m, 1468m, 1449m, 1370m, 1351m, 1128m, 1070m, 756m and 696m cm^{-1}; δH (WH 300) 1.13-2.07 (10H, m, CH_2 of ring), 3.26 (1H, m, NHCH), 4.35 (1H, br, NH), 7.20-7.55 (5H, m, Ph) and 7.64 (1H, s, HC=N; m/e (NH_3 C.I.) 202 (M^+, 62%), 159 (100), 119 (26), 105 (98), 77 (61), 56 (46), 55 (39) and 41 (37).

From BOC cyclohexylhydrazine and butanal:

Butanal cyclohexylhydrazone (41j) (51%, slightly impure) as a mixture of isomers E:Z ~3:1; b.p. 118-126°/20mmHg; ν_{max} (film) 3600-3100br w (N-H), 2965s, 2930s, 2860s, 1465m, 1453s, 1368m, 1348m, 1258m, 1118m, 918m and 893m cm^{-1}; δH (WH 300) 0.89-1.02 (3H, m, 4-C<u>H</u>$_3$), 1.03-2.04 (12H, m, C<u>H</u>$_2$ of ring, 3-C<u>H</u>$_2$), 2.10-2.18 (2H, m, 2-C<u>H</u>$_2$), 3.03-3.10 (1H, m, NHC<u>H</u>), 6.46 and 7.02 (1H, 2x t, <u>H</u>C=N); m/e (NH_3 C.I.) 169 (MH^+, 100%), 154 (10) and 116 (11), + higher m/e peaks.

General Procedure for the Preparation of Secondary Alkyl Hydrazones in Non-aqueous Solution

The following procedure is typical:

Preparation of Acetaldehyde Cyclohexylhydrazone (41a)

BOC cyclohexylhydrazine (6.95 g, 32mmol) was dissolved in a solution of hydrogen chloride in methanol (ca 6M, 40ml) and stirred until gas evolution ceased. The solution was concentrated and the crude hydrazine hydrochloride dissloved in methanol (50ml), triethylamine (30ml) and dichloromethane (50ml). Acetaldehyde (3.0ml, 48mmol) was added and the solution stirred under an inert atmosphere for 90 min.. The solution was concentrated, dissolved in dichloromethane (50ml) and washed with water (50ml). The aqueous layer was back-extracted with dichloromethane (2x 25ml), the organic layers combined, dried (sodium sulphate), filtered and concentrated. Distillation from calcium hydride gave the title hydrazone (41a) (53%); data as above.

Similarly Prepared:

From crude BOC DMP hydrazine (50) and acetaldehyde: Acetaldehyde DMP hydrazone (51a) (40%) as a mixture of isomers E:Z ~3:2; b.p. 50-52°/4mmHg; ν_{max} (film) 3600-3100br w (N-H), 2940s, 2910s, 2855s, 1594m, 1466m, 1436m, 1374m, 1359m, 1326m, 1152m, 1106m, 1087m, 1074s, 976m, 913m, 853m and 786m cm^{-1}; δH (QE 300) 0.89, 0.94 (12H, 2x d, J 7Hz, $CH(CH(C\underline{H}_3)_2)_2$), 1.70, 1.83 (3H, 2x d, J 5Hz, $C\underline{H}_3CH$), 1.86 (2H, m, $CH(C\underline{H}Me_2)_2$), 2.76, 2.81 (1H, t (J 6Hz) plus m, $C\underline{H}i\underline{P}r_2$), 4.92 (1H, br, N<u>H</u>), 6.37 and 6.93 (1H, 2x q, J 5Hz, $CH_3C\underline{H}$); m/e (E.I.) 156 (M^+, 3%), 127 (10), 113 (100), 71 (11), 70 (14), 57 (39), 43 (100) and 41 (51); analysis found C:69.0, H:13.3, N:18.2%; $C_9H_{20}N_2$ requires C:69.2, H:12.9, N17.9%.

From BOC DMP hydrazine (50) and acetone: Acetone DMP hydrazone (51b) (44%); b.p.119-121°/15mmHg; ν_{max} (film) 2960s, 2930s, 2910m, 2875m, 1470m, 1383m, 1363m and 1121m cm^{-1}; δH (WH 300) 0.89, 0.93 (12H, 2xd, J 7Hz, $CH(CH(C\underline{H}_3)_2)_2$), 1.71, 1.81 (6H, 2x s, $C\underline{H}_3C(=N)C\underline{H}_3$), 1.77-1.88 (2H, 2x m, $CH(C\underline{H}Me_2)_2$), 2.79 (1H, ca t, J 6Hz, $C\underline{H}i\underline{P}r$) and 4.41 (1H, br, N<u>H</u>); δC (AM 250) 14.78, 24.65 (2x q, $\underline{C}H_3C(=N)\underline{C}H_3$), 17.98, 20.50 (2x q, $CH(CH(\underline{C}H_3)_2)_2$), 29.77 (d, $CH(\underline{C}HMe_2)_2$), 69.62 (d, $\underline{C}H\underline{i}Pr_2$) and 139.26 (s, $\underline{C}$=N); m/e (E.I.) 170 (M^+, 6%), 127 (100), 113 (7), 70 (14), 58 (44), 56 (46), 43 (18) and 41 (14); M^+ (E.I.) found: 170.1783; $C_{10}H_{22}N_2$ requires: 170.1783.

From BOC DMP hydrazine (50) and propanal: Propanal DMP hydrazone (51k) (42%) as a mixture of isomers

E:Z ~3:2, b.p.51-52°/1mmHg; ν_{max} (film) 3600-3100br w (N-H), 2960s, 2925s, 2865s, 1464m, 1380m, 1364m, 1107m and 1088m cm^{-1}; δH (QE 300) 0.89-0.97 (12H, m, $CH(CH(CH_3)_2)_2$), 1.04, 1.14 (3H, 2x t, J 8Hz, 3-CH_2), 1.78-1.90 (2H, m, $CH(CHMe_2)_2$), 2.05-2.23 (2H, m, 2-CH_2), 2.75, 2.80 (1H, 2x t, J 6Hz, $CHiPr_2$), 6.20 and 6.92 (1H, 2x t, J 5Hz, 1-CH); m/e (E.I.) 170 (M^+, 2%), 127 (100), 72 (11), 70 (30), 58 (31), 55 (28), 43 (29) and 40 (24); M^+ (E.I.) found 170.1780 $C_{10}H_{22}N_2$ requires 170.1783.

From BOC DMP hydrazine (50) and phenylacetone:

Phenylacetone DMP hydrazone (511) (48%, slightly impure) as a mixture of isomers E:Z~3:1; b.p. 122-131 °/1.5mmHg; ν_{max} (film) 3075w, 3055w, 3020w, 2950s, 2920s, 2865s, 1599w, 1488m, 1463m, 1448m, 1379m, 1362m, 1174m, 1151m, 1108m, 1093m, 731m and 696s cm^{-1}; δH (QE 300) 0.78, 0.86, 0.93, 0.99 (12H, 4x d, J 7Hz, $CH(CH(CH_3)_2)_2$), 1.62, 1.98 (3H, 2x s, 3-CH_3), 1.72, 1.87 (2H, 2x m, $CH(CHMe_2)_2$), 2.76, 2.89 (1H, 2x t, J 6Hz, $CHiPr_2$), 3.51 (2H, s, $PhCH_2$), 4.64 (1H, br, NH) and 7.20-7.35 (5H, m, Ph); m/e (E.I.) 246 (M^+, 3%), 203 (100), 134 (23), 92 (36), 91 (100), 70 (11), 65 (25), 57 (19), 56 (11), 55 (12), 43 (43) and 41 (34).

Preparation of Pinacolone Hydrazone (60)

To pinacolone (25.03g, 0.25 mol) was added hydrazine hydrate (12.5ml) and t-butanol (10ml). The solution was refluxed for 3h. cooled and poured into water (200ml). The aqueous solution was extracted with ether (3x 60ml), the

organic layers combined, washed with brine, dried (sodium sulphate), filtered and concentrated. The crude hydrazone was distilled to give the title hydrazone[143] (60) (15.89g, 56%); b.p. 75-83°/25mmHg; ν_{max} (film) 3600-3100br m (N-H), 2980s, 2905m, 2870m, 1480m, 1463m, 1364m and 1151m cm^{-1}; δH (R24) 1.05 (9H, s, $C(C\underline{H}_3)_3$), 1.68 (3H, s, $N{=}CC\underline{H}_3$) and 4.75 (2H, br, $N\underline{H}_2$); m/e (E.I.) 114 (M^+, 8%), 99 (18), 82 (12), 72 (24), 57 (100), 41 (72) and 39 (47).

General Procedure for the Preparation of TBM hydrazones:

The following procedure is typical:

Preparation of (±) Acetaldehyde TBM hydrazone (61a)

To pinacolone hydrazone (60) (4.033g, 35mmol) was added THF (80ml), sodium cyanoborohydride (1.55g, 25mmol) and methyl orange (few mg). The solution was cooled to 0° and hydrogen chloride in methanol was added to produce pH 3. Further hydrogen chloride in methanol was added when required to maintain the reaction at pH 3. After 90min. the solution was concentrated to give the crude hydrazine hydrochloride (R24 CD_3OD; 1.02 (9H, s, $C(C\underline{H}_3)_3$), 1.26 (3H, d, J 7Hz, $CHC\underline{H}_3$) and 2.90 (1H, q, J 7Hz, $C\underline{H}CH_3$)). The crude hydrochloride was condensed with acetaldehyde using the non-aqueous conditions described above to give the title hydrazone (61a) (1.605g, 32%) as a mixture of isomers E:Z ~ 3:2; b.p. 67-71°/23mmHg; ν_{max} (film) 3540-3140br w (N-H), 2960s, 2910s, 2870s, 1480m, 1456m, 1445m, 1395m, 1372m, 1109m and 1065m cm^{-1}; δH (WH 300) 0.92, 0.93 (9H, 2x s, $C(C\underline{H}_3)_3$), 1.05, 1.09 (3H, 2x d, J 7Hz, $CHC\underline{H}_3$), 1.70, 1.85

(3H, 2x d, J 5Hz, 2-$C\underline{H}_3$), 3.02, 3.10 (1H, 2x q, J 7Hz, N-C<u>H</u>Me), 4.78 (1H, br, N<u>H</u>), 6.52 and 7.00 (1H, 2x q, J 5Hz, 1-C<u>H</u>); m/e (E.I.) 142 (M^+, 3%), 85 (100) and 43 (45); m/e (NH_3 C.I.) 143 (MH^+, 100%) and 85 (18), M^+ (E.I.) found: 142.1469; $C_8H_{18}N_2$ requires: 142.1470.

Similarly Prepared:

From pinacolone hydrazone (60) and acetone:

(±) Acetone TBM hydrazone (61b) (62%); b.p. 83-85°/23mmHg; ν_{max} (film) 3560-3020br m (N-H), 2960s, 2910m, 2875m, 1479m, 1462m, 1452m, 1373m, 1364m, 1207m and 1183m cm^{-1}; δH (WH 300) 0.93 (9H, s, $C(C\underline{H}_3)_3$), 1.06 (3H, d, J 7Hz, $CHC\underline{H}_3$), 1.71, 1.92 (6H, 2x s, $C\underline{H}_3C(=N)C\underline{H}_3$) and 3.03 (1H, q, J 7Hz, C<u>H</u>Me); m/e (E.I.) 143 (16%), 99 (100), 85 (24), 56 (42), 43 (37) and 41 (17); m/e (NH_3 C.I.) 157 (MH^+, 100%) and 99 (26).

General Procedure for the Alkylation of Secondary Alkyl Hydrazones

Hydrazone (3mmol) was dissolved in THF (7ml) and cooled to 0°. n-Butyl lithium (3.6mmol) was added and the reaction stirred for 10 min., then cooled to -78°. after 10 min. alkyl halide (4.5mmol) was added and the reaction allowed to warm to room temperature and then stir overnight. Water (10ml) and ether (20ml) were added and the layers separated. The aqueous layer was extracted with ether (2x 10ml), the organic layers combined, dried (sodium sulphate), filtered and concentrated. The crude product was

examined by 300 MHz n.m.r. spectroscopy.

Preparation of (±) 2-DMP azo-1-phenylpropane (52aa)

The general procedure for the alkylation of secondary alkyl hydrazones was followed using acetaldehyde DMP hydrazone (51a) and benzyl bromide. The crude material was chromatographed (75g silica, eluant ether:petroleum; 7:93) to give 0.583g crude azoalkane. Purification of a sample (198mg) by p.l.c. (3 plates, eluant toluene) gave the title azoalkane (52aa) (165mg, 65%); t.l.c. (toluene) R_f0.5; ν_{max} (film) 3080w, 3060w, 3025m, 2960s, 2925s, 2865m, 1600w, 1494m, 1465m, 1451m, 1383m, 1367m, 741m and 696s cm^{-1}; δH (QE 300) 0.69, 0.72, 0.85, 0.89 (12H, 4x d, J 7Hz, $CH(CH(C\underline{H}_3)_2)_2$), 1.26, (3H, d, J 7Hz, 3-$C\underline{H}_3$), 2.15-2.28 (2H, m, $CH(C\underline{H}Me_2)_2$), 2.67 (1H, t, J 6Hz, $C\underline{H}iPr_2$), 2.94-3.23 (2H, m, $C\underline{H}_2Ph$), 3.86-3.93 (1H, m, 2-C$\underline{H}$) and 7.16-7.29 (5H, m, Ph); δC (XL 100) 18.00, 18.18, 19.93, 20.09 (4x q, $CH(CH(\underline{C}H_3)_2)_2$), 18.77 (q, 3-$\underline{C}H_3$), 28.28, 28.46 (2x d, $CH(\underline{C}HMe_2)_2$), 41.42 (t, Ph$\underline{C}H_2$), 75.65, 88.11 (2x d, 2-$\underline{C}$H, $\underline{C}HiPr_2$), 125.91, 128.13, 129.26 (3x d, $\underline{C}$H of Ph) and 138.64 (s, $\underline{C}_{ipso}$); m/e (E.I.) 246 (M^+, 4%), 245 (12), 148 (17), 91 (47), 69 (34), 57 (100), 43 (73) and 41 (46); analysis found C:77.9, H:10.5, N:11.6%; $C_{16}H_{26}N_2$ requires C:78.0, H:10.6, N:11.4%.

Similarly Prepared:

From propanal DMP hydrazone (51k) and benzyl bromide: (±)2-DMP azo-1-phenylpropane (52ka) (46%), t.l.c. R_f0.5; ν_{max} (film) 3085w, 3060w, 3020m, 2955s, 2925s, 2865s, 1601w, 1492m, 1465m, 1458m, 1450m, 1382m, 1365m, 737m and 696s cm^{-}

^{1}; δH (QE 300) 0.68-0.71, 0.87-0.95 (15H, 2x m, $CH(CH(C\underline{H}_3)_2)_2$, and 4-$C\underline{H}_3$), 1.72-1.86 (2H, m, 3-$C\underline{H}_2$), 2.13-2.33 (2H, m, $CH(C\underline{H}Me_2)_2$), 2.68 (1H, t, $\underline{J}$ 6Hz, $C\underline{H}\underline{i}Pr_2$), 3.00-3.13 (2H, m, $C\underline{H}_2Ph$), 3.64-3.72 (1H, m, 2-$C\underline{H}$) and 7.19-7.28 (5H, m, Ph); δC (QE 300) 10.91 (q, 4-$\underline{C}H_3$), 18.19, 18.57, 20.14, 20.37 (4x q, $CH(CH(\underline{C}H_3)_2)_2$), 26.17 (t, 3-$\underline{C}H_2$), 28.65 (d, $CH(\underline{C}HMe_2)_2$), 39.84 (t, $\underline{C}H_2Ph$), 80.44, 88.65 (2x d, 2-$\underline{C}H$, $\underline{C}H\underline{i}Pr_2$), 126.13, 128.36, 129.57 (3x d, $\underline{C}H$ of Ph) and 138.94 (s, $\underline{C}_{ipso}$); m/e (E.I.) 260 (M^+, 0.3%), 259 (1), 145 (22), 131 (17), 91 (94), 57 (100), 43 (39) and 41 (15); M^+ found: 260.2240; $C_{17}H_{28}N_2$ requires: 260.2253.

From propanal DMP hydrazone (51k) and 1-iodobutane:

<u>(±)3-DMP azoheptane</u> (52kb) (74%); t.l.c. (toluene) R_f0.6; ν_{max} (film) 2955s, 2925s, 2880s, 1464m, 1456m, 1382m and 1366m cm^{-1}; δH (QE 300) 0.87-0.93 (18H, m, 6x $C\underline{H}_3$), 1.23-1.34 (4H, m, 5,6-$C\underline{H}_2$), 1.69-1.82 (4H, m, 2,4-$C\underline{H}_2$), 2.24-2.32 (2H, m, $CH(C\underline{H}Me_2)_2$), 2.72 (1H, t, $\underline{J}$ 6Hz) and 3.24 (1H, m, 3-$C\underline{H}_2$); δC (XL 100, BB only) 10.73, 13.94 (1,7-$\underline{C}H_3$), 18.34, 20.21 ($CH(CH(\underline{C}H_3)_2)_2$), 22.68, 26.49, 28.32, 32.70 (2,4,5,6-$\underline{C}H_2$), 28.49 ($CH(\underline{C}HMe_2)_2$), 79.18 and 88.40 (3-$\underline{C}H$, $\underline{C}H\underline{i}Pr_2$); m/e (E.I.) 226 ($M^+$, 0.5%), 225 (2), 99 (5), 57(100), 43 (37) and 41 (16); M^+ (E.I.) found 226.2388; $C_{14}H_{30}N_2$ requires 226.2409.

From (±) acetaldehyde TBM hydrazone (61a) and benzyl bromide:

<u>1-phenyl-2(R,S)-((R,S)TBM azo)-propane</u> (62aa) (47%) as a mixture of diastereoisomers -3:2; t.l.c. (petroleum:ether;

9:1) R_f0.5; ν_{max} (film) 3090w, 3070w, 3035m, 2965s, 2935s, 2910s, 2875s, 1499m, 1479m, 1454m, 1372m, 1365m, 751 and 702s cm^{-1}; δH (WH 300) 0.83, 0.92 (9H, 2x s, $C(C\underline{H}_3)_3$), 0.96,1.05 (3H, 2x d, J 7Hz, t-$BuCHC\underline{H}_3$), 1.21, 1.25 (3H, 2x d, J 7Hz, $PhCH_2CHC\underline{H}_3$), 2.88-2.96, 3.11-3.19 (2H, 2x m, $PhC\underline{H}_2$), 3.04,3.05 (1H, 2x q, J 7Hz, t-$BuC\underline{H}Me$), 3.76-3.87 (1H, m, $PhCH_2C\underline{H}Me$) and 7.15-7.29 (5H, m, Ph); δC (AM 250) 13.71, 13.86, 18.27, 18.42 (4x q, 2x $CH\underline{C}H_3$), 26.54, 26.59 (2x q, $C(\underline{C}H_3)_3$), 33.48, 33.66 (2x s, $\underline{C}Me_3$), 41.27, 41.35 (2x t, $Ph\underline{C}H_2$), 73.45, 73.50, 80.91 (2x d plus another d, t-$Bu\underline{C}HMe$, $PhCH_2\underline{C}HMe$), 126.00, 128.12, 128.21, 129.38, 129.46 (5x d, $\underline{C}H$ of Ph) and 138.81 (s, $\underline{C}_{ipso}$); m/e (E.I.) 232 (M^+, 1%), 187 (3), 119 (9), 91 (43), 85 (42), 57 (16), 42 (100) and 40 (23), m/e (NH_3 C.I.) 233 (MH^+, 100%), 187 (4) and 91 (7).

From (±) acetone TBM hydrazone (61b) and benzyl bromide: (±) 2-Methyl-1-phenyl-2-(TBM azo)propane (62ba) (73%), t.l.c. (toluene) R_f0.5; ν_{max} (film) 3085w, 3065w, 3030m, 2965s, 2930s, 2870m, 1494m, 1479m, 1453m, 1392m, 1378m, 1362m, 1206m, 744m, 720m and 702s cm^{-1}; δH (WH 300) 0.93 (9H, s, $C(C\underline{H}_3)_3$), 1.05 (3H, d, J 7Hz, $CHC\underline{H}_3$), 1.09, 1.16 (6H, 2x s, $C(C\underline{H}_3)_2$), 2.96 (2H, s, $PhC\underline{H}_2$), 3.11 (1H, q, J 7Hz, $C\underline{H}Me$) and 7.14-7.28 (5H, m, Ph); δC (AM 250) 13.81, 24.45, 24.73 (3x q, $CH\underline{C}H_3$, $C(\underline{C}H_3)_2$), 26.68 (q, $C(\underline{C}H_3)_3$), 33.76 (s, $\underline{C}Me_3$), 46.59 (t, $Ph\underline{C}H_2$), 69.88 (s, $\underline{C}Me_2$), 80.65 (d, $\underline{C}HMe$), 125.99, 127.67, 130.62 (3x d, $\underline{C}H$ of Ph) and 138.22 (s, $\underline{C}_{ipso}$); m/e (E.I.) 145 (6%), 133 (45), 91 (100), 85 (18), 55 (19), 42 (52) and 40 (20); m/e (NH_3 C.I.) 247

(MH^+, 100) and 91 (8).

From (±) acetone TBM hydrazone (61b) and 1-iodoheptane: (±) 2-methyl-2-(TBM azo)nonane (62bc) (68%); t.l.c. (petroleum:ether; 9:1) R_f0.8; ν_{max} (film) 2965s, 2930s, 2875s, 2860s, 1466m, 1380m, 1370m and 1364m cm^{-1}; δH (WH 300) 0.88 (3H, t, J 7Hz, 9-CH_3), 0.95 (9H, s, $C(CH_3)_3$), 1.04 (3H, d, J 7Hz, $CHCH_3$), 1.10, 1.14 (6H, 2x s, $C(CH_3)_2$), 1.24-1.28 (10H, br, 4,5,6,7,8-CH_2), 1.60-1.65 (2H, m, 3-CH_2) and 3.04 (1H, q, J 7Hz, CHMe); δC (AM 250) 13.95, 14.07, 24.57, 24.85 (4x q, $CHCH_3$, $C(CH_3)_2$, 9-CH_3), 22.66, 24.01, 29.27, 30.32, 31.86, 40.65 (6x t, 3,4,5,6,7,8-CH_2), 26.69 (q, $C(CH_3)_3$), 33.67 (s, CMe_3), 69.09 (s, CMe_2) and 80.70 (d, CHMe); m/e (E.I.) 141 (9%), 85 (41), 71 (33), 57 (72), 42 (100) and 40 (26); m/e (NH_3 C.I.) 255 (MH^+, 100).

Preparation of (±)-1-hydroxy-1-phenylpropan-2-one (54a)

To a solution of acetaldehyde DMP hydrazone (51a) (0.800g, 5.0mmol) in THF (8ml) at 0° was added n-butyl lithium (5.5mmol) and the reaction stirred for 10min.. Benzaldehyde (0.6ml, 6.0mmol) was added and the reaction stirred for 15min.. n-Butyl lithium (6.0mmol) was added, the reaction stirred for 15min., quenched with water (0.5ml) and ether (30ml) was added. The solution was washed with brine (10ml), the brine layer extracted with ether (10ml), the ether layers combined, dried (sodium sulphate), filtered and concentrated. Hydrolysis (method A, work up A) gave 1.614 crude material. Purification of a sample (266mg)

by p.l.c. (3 plates, eluant ether:dichloromethane; 1:9) gave the title hydroxyketone (54a) (46mg, 36%); t.l.c. (ether: dichloromethane; 1:9) R_f0.6; ν_{max} ($CHCl_3$) 3640-3290br m (O-H), 2960m, 2935m, 2875m, 1714s (C=O), 1495m, 1454m, 1361m, 1091m and 1069m cm^{-1}; δH (WH 300) 2.10 (3H, s, $C\underline{H}_3$), 4.31 (1H, d, J 4Hz, O$\underline{H}$), 5.11 (1H, d, J 4Hz, C$\underline{H}$OH) and 7.32-7.43 (5H, m, Ph), identical to authentic sample[56].

Similar reaction with (±) acetaldehyde TBM hydrazone (61a) and benzaldehyde gave the same hydroxyketone (54a) (23%) (identical properties).

Preparation of (2-methyl-1-phenylprop-2-yl)hydrazine hydrochloride (56ba)

Acetone DMP hydrazone (51b) was alkylated under the standard conditions with benzyl bromide to give:

2-DMP azo-2-methyl-1-phenylpropane (52ba) (not isolated, δH (WH 300, on crude reaction product) 0.87 (12H, ca t, J 7Hz, $CH(CH(C\underline{H}_3)_2)_2$), 1.16 (6H, s, $C(C\underline{H}_3)_2$), 2.20-2.38 (2H, m, $CH(C\underline{H}Me_2)_2$), 2.76 (1H, t, J 7Hz, $C\underline{H}iPr_2$), 2.96 (2H, s, $PhC\underline{H}_2$) and 7.19-7.42 (5H, br, Ph)). The crude azoalkane (52ba) was stirred with TFA (2ml) for 5h. to give:

2,4-Dimethylpentanone (2-methyl-1-phenylprop-2-yl)hydrazone (55ba) (not isolated, δH (WH 300, on crude reaction product) 1.12, 1.27 (12H, 2x d, J 7Hz, 2x $CH(C\underline{H}_3)_2$), 1.44 (6H, s, $C(C\underline{H}_3)_2$), 2.90, 3.13 (2H, 2x septet, J 7Hz, 2x $C\underline{H}Me_2$), 3.03 (2H, s, $PhC\underline{H}_2$) and 7.15-7.42 (5H, m, Ph)). The crude hydrazone (55ba) was hydrolysed with hydrochloric acid (concentrated, 5ml) in ethanol (5ml) for 16h.. The

solution was washed with ether (3x 10ml) and the aqueous layer concentrated. Recrystallisation from ethereal ethanol gave (2-methyl-1-phenylprop-2-yl)hydrazine hydrochloride (56ba) (0.172g, 17%) as an unstable solid, stored at -20°; m.p. 137-139° (lit.[160] 139-141°); ν_{max} (KBr) 3290s (N-H), 3180s (N-H), 3085m, 3065m, 3030m, 2970s, 2870s, 2770s, 2685s, 2585m, 2480s, 1624m, 1588m, 1577m, 1493m, 1469m, 1453m, 1392m, 1379m, 1315m, 1167m, 1145m, 1129m, 1104m, 1072m, 942m, 935m, 917m, 766m, 726m, 719m and 697s cm^{-1}; δH (WH 300, CD_3OD) 1.24 (6H, s, $C(C\underline{H}_3)_2$, 2.94 (2H, s, $PhC\underline{H}_2$) and 7.21-7.38 (5H, m, Ph); δC (AM 250, CD_3OD) 22.12 (q, $C(\underline{C}H_3)_2$), 43.54 (t, $Ph\underline{C}H_2$), 62.91 ($\underline{C}NH$), 128.35, 129.52, 131.74 (3x d, $\underline{C}H$ of Ph) and 136.02 (s, $\underline{C}_{ipso}$); m/e (NH_3 D.C.I.) 165 ($C_{10}H_{17}N_2^+$, 100%) and 73 (19).

Reaction of (±) 2-(DMP azo)-1-phenylpropane (52aa) with TFA

(±) 2-(DMP azo)-1-phenylpropane (52aa) was stirred with TFA (3ml) for 5h.. The TFA was removed by concentration to give Phenylacetone DMP hydrazone (511) as a mixture of isomers E:Z ~3:1; δH (WH 300) identical to authentic material (p121).

Reaction of (±) 2-Methyl-1-phenyl-2-(TBM azo)propane (62ba) with TFA

(±) 2-Methyl-1-phenyl-2-(TBM azo)propane (62ba) was stirred with TFA (3ml) for 5h.. The TFA was removed by concentration to give Pinacolone (2-methyl-1-phenylprop-2-yl)hydrazone (65ba) (not isolated, δH (R 24) 1.13 (9H, s, $C(C\underline{H}_3)_3$), 1.41 (6H, s, $C(C\underline{H}_3)_2$), 2.08 (3H, s, $C\underline{H}_3C{=}N$), 2.96

(2H, s, $PhC\underline{H}_2$) and 7.21-7.40 (5H, m, Ph).

Reaction of 1-phenyl-2-(R,S)-((R,S)-TBM azo)propane (62aa) with TFA

Azoalkane (62aa) was stirred with TFA (3ml) for 4h.. The TFA was removed by concentration. Examination of the crude product by n.m.r. spetroscopy (WH 300) showed a complex product, in contrast to previous TFA tautomerisations. Resonances assigned to both (±) Pinacolone (1-phenylprop-2-yl)hydrazone (65aa) (1.18, 1.23, 2x s, $C(C\underline{H}_3)_3$; 2.05, 2.07 $C\underline{H}_3C{=}N$, ~1:2 mixture of isomers) and (±) Phenylacetone TBM hydrazone (611) (1.02, s, $C(C\underline{H}_3)_3$; 1.15, d, J 7Hz, $CHC\underline{H}_3$; 2.23, 2.37, 2x s, $C\underline{H}_3C{=}N$; and 3.78, 3.93 2x s, $PhCH_2$, ~2:3 mixture of isomers). (65aa):(611) ~2:1, but many other resonances could not be assigned.

General Procedure for the Preparation of Alkylhydrazine Hydrochlorides from TBM Azoalkanes

The following procedure is typical:

Preparation of (2-Methyl-1-phenylprop-2-yl)hydrazine Hydrochloride (56ba) From (±)-2-Methyl-1-phenyl-2-(TBM azo)propane (62ba)

Azoalkane (62ba) (114mg, 0.46mmol) was dissolved in ether (2ml) and stirred for 16h. with hydrochloric acid (2M, 2ml). The layers were separated, the aqueous layer was washed with ether (2x 1.5ml) and concentrated. Recrystallisation from ethyl acetate-ether gave the title hydrazine hydrochloride (56ba) (35mg, 38%); m.p. 135-136°, δH (WH 300) as before.

Similarly Prepared:

From (±) 2-Methyl-2-(TBM azo)nonane (62bc) (153mg, 0.6mmol):

(2-Methylnon-2-yl)hydrazine hydrochloride (66bc) (14mg, 11%); m.p. 86.5-87°; ν_{max} (KBr) 3260m (N-H, 3175m (N-H), 2955s, 2925s, 2870s, 2855s, 2780m, 2500m (N-H), 1634m (N-H), 1594m (N-H), 1467m, 1392m, 1373m, 1162m, 1145m and 964m cm^{-1}; δH (WH 300, CD_3OD) 0.91 (3H, t, J 7Hz, 9-CH_3), 1.28 (6H, s, $C(CH_3)_2$), 1.31-1.36 (10H, br, 4,5,6,7,8-CH_2) and 1.58-1.63 (2H, m, 3-CH_2); m/e (E.I.) 172 ($C_{10}H_{24}N_2^+$, 6%), 157 (11), 73 (100), 57 (23), 56 (18), 42 (27) and 40 (23).

Preparation of 2-Methyl-1-phenylprop-2-ylamine Hydrochloride (67ba)

Hydrazine hydrochloride (66ba) (51mg, 0.25mmol) was dissolved in ethanol (10ml). Raney-nickel (2g, previously washed with ethanol, 4x 5ml) and hydrazine (anhydrous, 2ml) were added and the reaction was stirred until gas evolution ceased. The Raney-nickel was removed by filtration through celite and the resulting solution concentrated to leave a solid which was recrystallised from ethyl acetate-ether to give the title amine hydrochloride (67ba)[161] (25mg, 53%); m.p. 196-7° (lit.[161]:200°;[162]:195-6°); δH (WH 300, CD_3OD) 1.33 (6H, s, $C(CH_3)_2$), 2.92 (2H, s, $PhCH_2$) and 7.22-7.42 (5h, m, Ph).; m/e (I.B.E.I.) 134 (6%), 91 (9) and 58 (100); m/e (NH_3 D.C.I.) 150 (MH^+, 100%) and 58 (45). (A sample doped with authentic 2-methyl-1-phenylprop-2-ylhydrazine

hydrochloride (66ba) showed two singlets each in both the methyl region and the benzylic methylene region.)

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